Why Clinical Practice Guidelines Shift Over Time:
A Dynamic Model with Application to Prostate Cancer Screening

by

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Abstract

Essay 1: A Dynamic Model for Understanding Long-Term Trends in Prostate Cancer Screening

Cancer remains the second leading cause of death in the U.S. after heart disease. After 35 years of routine cancer screening, we still have only a limited understanding of screening dynamics. There is evidence of over-screening and resulting overtreatment in certain cases, and significant provider variation and fluctuations over time in screening criteria. Here I present empirical data for fluctuations in official screening guidelines and in actual practice for the use of the prostate-specific antigen (PSA) test. I explore how these dynamics are affected by the main guideline-issuing organizations in the U.S. and by clinicians, patient groups, and the media.

Essay 2: Our Walk to the End of Cancer? Understanding Long-Term Trends in Medical Screening

In this study we develop the first integrated, broad boundary feedback theory and formal model to explain the dynamics of medical screening. The theory includes a decision-theoretic core around harms and benefits including the fundamental tradeoff between sensitivity and specificity; and feedbacks that condition guidelines and actual practice. To provide context we use the case of PSA screening for prostate cancer as a motivating example, but our model is generic and applicable to other contexts. We present a behaviorally realistic, boundedly-rational model of detection and selection for health screening that creates oscillations in policy recommendation thresholds of formal guidelines. This core model, entailing only the evidence generation and translation processes, demonstrates how oscillations are natural to this category of problems due to inherent delays in evidence-based screening. These fluctuations lead to long periods during which screening guidelines are suboptimal.

Essay 3: A Dynamic Model for Understanding Long-Term Trends in Prostate Cancer Screening

Whereas guidelines for routine screening should be based on medical evidence, evidence often has relatively little impact on practice. This situation has led to ongoing controversy and conflict over appropriate guidelines among scientists, clinicians, and patient advocacy groups. There are significant variations in clinical practice, including evidence of over-screening for some diseases, and under-screening for others. To explain the patterns of over-screening, fluctuations, low adherence to guidelines, and conflict, I develop the first explicit broad boundary feedback theory of the dynamics of medical screening, tested in a formal mathematical model. The model presents an extended case study specific to PSA screening for prostate cancer, including realistic presentations for the fundamental tradeoff between test sensitivity and specificity, the natural progression of the disease, and respective changes in population size and composition.

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Table of Contents

8

List of Figures

Essay 3: List of Figures

List of Tables

Overview of Three Essays

The implications of widespread population screening for disease remain controversial. Whereas guidelines for routine screening should be based on medical evidence, evidence often has relatively low impact on practice, and this has led to ongoing controversy and conflict over appropriate guidelines among scientists, clinicians, and patient advocacy groups. There are significant variations in clinical practice, including evidence of over-screening for some diseases (e.g., breast and prostate cancer) and under-screening for others (e.g., colonoscopy). Furthermore, for several important diseases, the breadth indications for screening (treatment eligibility) have fluctuated over time, including age of initiation for routine screening and thresholds for a positive test result (indicating a need for biopsy or treatment).

Existing studies focus on the medical evidence supporting different screening guidelines but usually neglect the broad boundary processes that condition the adoption of and adherence to evidence-based guidelines by clinicians, advocacy groups, and patients. The aim of this study is to construct a sound theoretical framework to document evidence of reasons for the observed variations in guidelines, actual practice, and the gaps between them. To put things in context, I also explore this heterogeneity across different countries (such as the U.S. vs. the U.K.) and across different screening tests for other diseases (such as PSA test vs. mammography). Using both qualitative and quantitative evidence, I document variations in guidelines and actual practice across these dimensions.

To explain the patterns of over-/under-screening, fluctuating guidelines, low adherence to guidelines, and conflict between scientists and other groups, I develop the first explicit broad boundary feedback theory of the dynamics of medical screening, tested in a formal mathematical model. The model includes a behavioral theory explaining how guidelines change over time in response to changes in the evidence on the costs and benefits of screening, which in turn depend on the fundamental tradeoff between test sensitivity and specificity, and on the natural progression of the disease and changes in population size and composition. I provide a behavioral model of the decisions to alter guidelines for the appropriate age for screening and the threshold indicating a positive test result that includes the influence of common errors and biases in judgment and decision making (e.g., overemphasis on salient data) and social influences such as the role of patient advocacy and clinician groups.

To provide context I use the Prostate Specific Antigen (PSA) case as a motivating example, but the model is generic and applicable to other contexts such as mammography screening for breast cancer. Eventually I aim to expand the boundaries of the classical evidence-based model to create a more realistic life setting, including the influence of the socio-political environment where the actual screening decision is embedded. More specifically, I will look at how medical professional societies— including radiologists, patient advocacy groups, and other principal actors—influence the adoption and diffusion dynamics of medical screening in the U.S. context.

The objective of the first of these three essays is to set up the two main reference modes observed in clinical practice guidelines (CPG's) and the actual screening practice. This empirical piece includes an extensive literature search to document the most important timeline events, including important changes in FDA regulations, landmark publications that caused a change in the scientific evidence

base, cancer industry-related news, and the establishment of important organizations and disease awareness events in the U.S. in the late 1980's and 90's, together with any other milestone events. It also includes an important empirical data collection part on policy action thresholds (e.g., breadth indications of screening) of PSA screening guidelines. For this chapter, data are presented for both the starting and stopping ages to screen and the PSA decision threshold to send the patient to biopsy (the biopsy referral threshold). This chapter will be the foundation upon which our dynamic theory is based.

In essay two I present a behaviorally realistic, boundedly-rational model of detection and selection for health screening that creates oscillations in policy recommendation thresholds of formal guidelines. This stylized core model, entailing only the evidence generation and translation processes, demonstrates how oscillations are natural to this category of problems due to inherent delays in evidence-based screening.

In essay three I present an extended case study specific to the PSA screening for prostate cancer. Our end goal is to build a sound dynamic theory firmly grounded in empirical evidence and data to explain fluctuations in screening thresholds, and to document evidence of reasons for gaps between practice and evidence. After having established the underlying structure responsible for overshoot and undershoot of indications for screening (a normal but undesired adaptive condition of the internal environment), ways of monitoring, diagnosing, and managing these conditions can also be investigated. In the context of PSA screening for prostate cancer, breadth indications of screening include the PSA cutoff for ordering a biopsy, frequency of screening, and the recommended starting and ending ages for screening.

To summarize, my objective is to construct an empirically grounded theoretical framework to document the long-term effects and unintended consequences of changing disease definitions on published screening guidelines, and consequently on the actual practice; the specific mechanisms that influence differential implementation of these guidelines; the mechanisms which account for the gap (if any) between the scientific evidence and the actual practice of screening in two case studies (PSA screening and mammography); and ultimately to provide a formal simulation tool to explain the natural overshoots and undershoots in breadth indications of screening to potentially suggest policy measures to try to dampen them in the long term.

Essay 1: Understanding the Dynamics of Cancer Over-Screening and Fluctuations in Screening Criteria

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Abstract

Cancer remains the second leading cause of death in the U.S. after heart disease. After 35 years of routine cancer screening, we still have only a limited understanding of screening dynamics. There is evidence of over-screening and resulting overtreatment in certain cases, and significant provider variation and fluctuations over time in screening criteria. Here I present empirical data for fluctuations in official screening guidelines and in actual practice for the use of the prostate-specific antigen (PSA) test. I explore how these dynamics are affected by the main guideline-issuing organizations in the U.S. and by clinicians, patient groups, and the media.

Keywords:

Health screening, evidence-based screening, population based screening, clinical practice guidelines, guideline development, disease (or policy) threshold, screening controversy, over-screening, computer simulation, system dynamics, medical decision-making, PSA screening

Introduction

Routine health screening technologies such as mammography, and tests for diseases like diabetes and various types of cancers play an important role in public health. In 1968 the World Health Organization published a paper on the *Principles and Practice of Screening for Disease*, where ten fundamental principles were suggested to be met before the implementation of a screening program (Wilson and Junger, 1968). Based on these criteria, population or mass screening works best when:

1. The condition sought should be an important health problem;
2. There should be an accepted treatment for patients with recognized disease, and treatment should be better at an earlier stage;
3. Facilities for diagnosis and treatment should be available;
4. There should be a recognizable latent or early symptomatic stage;
5. There should be a suitable test or examination;
6. The test should be acceptable to the population;
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood;
8. There should be an agreed-upon policy on whom to treat as patients;
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole;
10. Case-finding should be a continuing process and not a "once and for all" project.

There is no doubt that screening for certain diseases, particularly among those deemed to be at high risk for those conditions, can save lives. Perhaps the best example is flexible sigmoidoscopy and colonoscopy screening for colon cancer, where there is a strong evidence base supporting the efficacy of the test. Studies show that people who receive regular sigmoidoscopy screening after age 50 have a 60-70 percent lower risk of mortality (Elmunzer et al., 2012; Schoen et al., 2012; Atkin et al., 2010).

Problem Definition and Objectives

The classical approach to setting evidence-based screening guidelines is based on the statistical paradigm of Type-I and Type-II errors, seeking to find an evidence-based balance between sensitivity (and thus the risk of false positives) and specificity (and the risk of false negatives), given the costs and benefits of different outcomes. This is the first step in decision making, involving only the available scientific evidence, which is the same for all decision makers.

Despite this ubiquitous nature of the evidence base, there is significant variation in clinical practice guidelines (CPG's) in the U.S., which is very puzzling. In the last few decades major health organizations have been recommending changes in several common disease definitions that mainly resulted in the expansion of the eligibility criteria for disease, with an apparent increase in disease incidence and prevalence. Based on 2010-2012 data 39.6% of Americans will be diagnosed with some kind of cancer at some point during their lifetime (National Cancer Institute, 2016), which is of

particular concern with a growing aging population. CPG's for various diseases still differ with respect to their breadth indications for screening, which themselves have been fluctuating over time:

Table 1 Recent Changes in Practice Guidelines

Change in Practice Guideline	Direction of Change in Breadth Selection Criteria	News Coverage
Cholesterol (2013)	Narrowing; doctors should not put most people on cholesterol-lowering medications like statins based on cholesterol levels alone	Bumps in the Road to New Cholesterol Guidelines Don't Give More Patients Statins
Hypertension (2014)	Narrowing the breadth selection criteria	Hypertension Guide May Affect 7.4 Million Hypertension Guidelines Can Be Eased, Panel Says
Common knee surgery (2013)	Narrowing, suggesting that it helps only very little for some people	Common Knee Surgery Does Very Little for Some, Study Suggests
Screening Mammography (2013)	Narrowing, especially for women in their 40's and 70's	New Guidelines on Breast Cancer Draw Opposition Panel Urges Mammograms at 50, Not 40 Mammogram Recommendations Spark Controversy, Confusion Our Feel-Good War on Breast Cancer
Prostate Screening (2012)	Narrowing the breadth selection criteria	Prostate Cancer Screening Still Not Recommended for All Prostate Screening Guidelines Are Loosened
Routine Pelvic Exam (2014)	Narrowing the breadth selection criteria	Guideline Calls Routine Pelvic Exams Unnecessary

There may be several reasons for the observed variations in guidelines and fluctuations in disease definitions. Guidelines may fluctuate because the underlying situation may reveal an evidence change in a fluctuating way, corresponding to exogenous shocks. This would result in variations in policy action thresholds which can be explained by an externally imposed function, such as responses to exogenous shocks arising from new scientific information, evidence provided by clinical studies and Randomized Controlled Trials (RCT's).

One can imagine another world where guidelines still fluctuate when there are no corresponding objective changes in the benefit-and-harm environment or other technologies that would motivate a legitimate change. In this case I may see fluctuations as a result of a potentially endogenous structure

that may include delays between generating and assimilating scientific evidence and other basic limitations and biases in judgment and decision-making.

In order to explore these possibilities, it is important to identify and document the roles that different actors have in affecting these dynamics. My main focus is to understand the different sources of variation in screening guidelines and actual practice, as well as other sources of heterogeneity, by collecting empirical data and gathering different expert opinion perspectives surrounding the screening decision. I will use the Prostate Specific Antigen (PSA) testing for prostate cancer as the primary case study. Major actors for PSA screening include clinicians, patient and advocacy groups, media and news pieces, and guideline-issuing organizations such as the U.S. Preventive Services Task Force (USPSTF), American Cancer Society (ACS), American Urological Association (AUA), and the National Cancer Coalition Network (NCCN).

Background

Basic Limitations and Biases in Judgment and Decision Making

As in most other dynamically complex situations, the decision of doctors to offer, and of patients to seek, screening is made with limited information about the test's potential benefits and harms. A corollary of limited availability of information is that it makes impossible for anyone to construct a fully comprehensive model of the decision-making situation including the relevant parameters and relationships between them (Radford, 1977). Incompleteness and inaccuracies eventually lead to incomplete mental models for all actors, implying "bounded rationality" (Simon, 1956).

Humans often make poor decisions in dynamically complex situations, and they do even worse when potential outcomes are associated with uncertainty, resulting in sub-optimal performance (Brehmer, 1989, 1992; Brehmer and Allard, 1991; Dorner 1989, 1996; Brehmer and Dorner, 1993; Kleinmunz, 1985; 1990; Kleinmuntz and Thomas, 1987; Kleinmuntz and Schkade, 1993; Schkade and Kleinmuntz, 1994; Dietrich et al., 2002; Sterman, 1989a, 2008, 2010, 2011). Dynamic decision making is difficult, especially when the decisions have multiple, delayed, indirect, and nonlinear effects described by multiple feedback processes (Sterman, 2002) – factors that hinder learning. Yet these are the situations in which both the policy makers and the public must act.

Prior research shows that learning is very slow in dynamic decision-making environments, even after trials are repeated, or additional time or incentives are provided (Diehl & Sterman, 1995; Moxnes, 2004; Sterman, 1989a, 1989b; Paich and Sterman 1993). People have difficulties with correctly inferring the results of the long-term consequences of their own actions in complex situations (Dorner 1975; Dorner and Reither 1978; Dorner 1980, 1989, 1996; Brehmer and Allard 1991; Sterman 1989). Sterman (1989) uses the term "misperception of feedback" to describe decision behavior in dynamic environments in which decisions feed back to alter the situation (Moxnes 1998, 2000, 2004).

When placing orders in Beergame, subjects are found to consistently "misperceive" feedback through the environment from their own past decisions, resulting in over- or under- ordering and instabilities throughout the supply chain. Following the game, players almost always attribute such instability to

the exogenously changing customer demand and not to their own decisions, while the real customer demand in fact is a constant, corresponding to a single step increase in customer orders. .

More recent research shows that humans make consistent errors even in the simplest possible dynamic systems without feedback, time delays, or nonlinearities, and fail to see the long-term results of the consequences of their actions (e.g., Booth Sweeney and Sterman, 2000; Cronin & Gonzalez, 2007; Sterman and Booth Sweeney, 2007; Cronin, Gonzalez and Sterman 2009; Pala and Vennix 2005; Rahmandad, 2008; Rahmandad, Repenning and Sterman, 2009). Research shows that people – even highly educated adults – fail to comprehend and learn in those situations. Rather, they often use some heuristics (or "rules of thumb") to simplify dynamic situations, which is efficient but may also be responsible for consistent judgmental errors (e.g., the correlation heuristic, the availability heuristic, the affect heuristic, anchoring on selected aspects of a problem, insensitivity to sample size, confirmation bias, failure to account for regression to the mean, salience bias, and the conjunction fallacy; see Chapman, 1967; Kahneman and Tversky, 1972, 1982; Tversky and Kahneman, 1973; Nickerson, 1998; Kunda, 1999; Slovic, 2006)

The difficulty lies in the inadequate human ability to comprehend and respond to complex and risky situations. Humans are poor judges of risk, and often behave in what can be considered as "irrational" ways instead of rationally maximizing the expectation of a utility function (Kahneman and Tversky, 1979; Tversky and Kahneman, 1991; Kahneman, 2011). Behavioral research sheds some light on perceptions of risk across different hazard domains, and on how people weigh features of these hazards (e.g., event type, intensity, proximity to event). Paul Slovic and colleagues have done extensive research in the domain of risk perception (Slovic, 2013, 1987) where they used tools from decision theory to show that affect has a dual role (system 1: fear, sadness, anger, mood, and other emotions) and deliberation (system 2: analysis of consequences of actions, and probabilities) (Mukherjee, 2010). Affect and emotion have been studied for a long time, yet the effects of affective processes on judgment and decision making remain relatively unexplored. More recently, research is being conducted to develop and test affect-based theories of judgment and decision making, to understand perceptual differences across hazard domains, and to collect longitudinal data across multiple hazards to build simulation tools for research and training.

Empirical Data: Methods

The following methods were employed:

1- An extensive medical literature search to document important events in the timeline of PSA guideline development;
2- Empirical data collection on how PSA screening criteria have evolved over time;
3- Expert opinion interviews as means of collecting parts and pieces of empirical data, and to seek support for the dynamic theory.

For the literature search for the PSA timeline and the empirical data collection for clinical practice guidelines I employed various data sources and news outlets. Practice guidelines were identified by a computerized search of the MEDLINE and Web of Science databases from 1986 through 2014, using the following subject terms: PSA screening, prostate cancer, early detection, practice guidelines, position statement. I also conducted a separate search using the name of four major guideline-issuing

organizations, including the USPSTF, ACS, AUA, and the NCCN. For news pieces, I collected the news headline results from Google trends, and conducted a manual search of the most important papers and commonly cited references. All citations recovered were imported into an open source bibliographic database (Zotero, Center for History and New Media, George Mason University).

Literature Search/ Timeline Events

Prostate cancer is the most frequently diagnosed cancer after (non-melanoma) skin cancer and the second leading cause of death from cancer in men in the United States; it is a disease that kills almost 30,000 American men every year (Siegel et al., 2011).

I conducted an extensive medical literature search on the history of PSA screening for prostate cancer, including major events, legal issues, news pieces, most-cited landmark publications causing a change in medical practice, and other milestone events. The timeline, together with a summary of major events and PSA Screening guidelines, can be found in Figure 2 (See also APPENDIX A). The extended timeline with all major events and changes in guidelines can be found in the supplementary material online.

The extended PSA timeline has about 150 entries under eight major categories of events: 1- Disease Awareness events: 16 entries, 2-Landmark papers that may have caused a change in medical practice: 12 entries, 3- Changes in Clinical Practice Guidelines of guideline issuing organizations: 40 entries, 4- Prostate cancer related FDA regulations: 9 entries, 5-Prostate cancer industry related events, and legal issues: 15 entries, 6-Important news pieces that appeared in newspaper and magazines: 16 entries, 7-Major changes in technology: 6 entries, 8- Other milestone events: 17 entries.

The National Cancer Act passes, which starts the "War on Cancer."
The American Cancer Society played a leading role in the passage of this act, considered one of the most dramatic pieces of health legislation ever enacted. It led to federal funding for cancer research rising from $4.3 million in 1953 to an estimated $5.1 billion in 2012.

Figure 1 First event on the timeline, The National Cancer Act Passes, which starts the "War on Cancer "in the United States

Dissemination of the PSA blood test: The Prostate Specific Antigen (PSA) was first identified by Prof. Richard Ablin in 1970 as a biomarker of the prostate gland (Ablin et al., 1970). Before the advent of the PSA test, prostate cancer (PCa) was usually diagnosed clinically with a digital rectal examination (DRE), which often detected cancer only after the disease had spread (Thompson et al., 2004). If a DRE was considered to be abnormal, a prostate biopsy was indicated, often with four or

19

fewer biopsy samples obtained. The morbidity associated with the procedure was substantial (Ruebush, 1979). In 1988, the use of ultrasound-guided biopsies with an automated, 18-gauge biopsy gun increased the safety and speed of the technique, causing a major change in medical practice (Lee et al., 1985; Ragde et al., 1988). Another major technological change was the development of nerve-sparing techniques for radical prostatectomy, which greatly increased the rates of surgery in the 1980's (Etzioni et al., 2012).
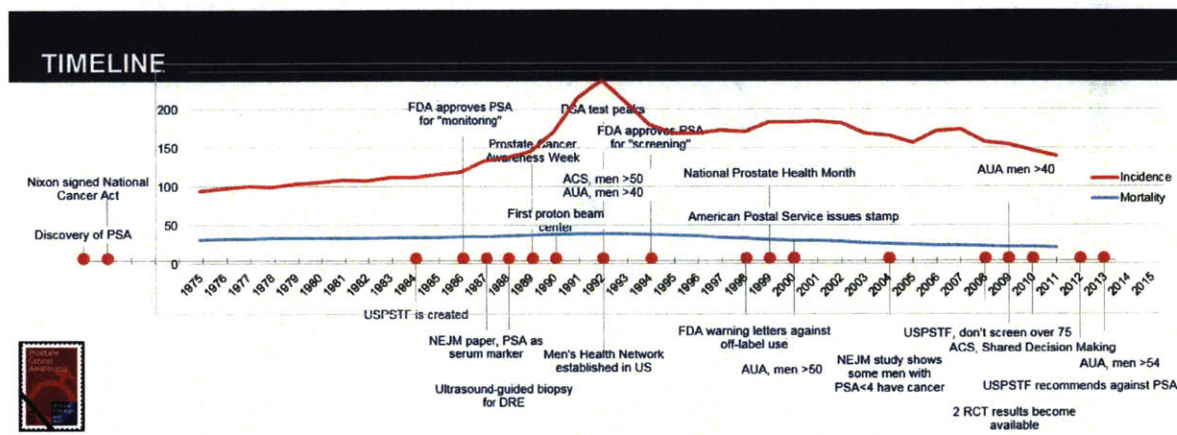
Figure 2 PSA timeline with selected major events, red and blue lines show prostate cancer incidence/ mortality per 100.000 men

Historically, the PSA test has been used for two purposes: 1- To aid doctors in treating men who have cancer and to identify recurrence rates following treatment (FDA approved in 1986), and 2- As a screening test in healthy men to help detect cancer (Charatan, 1994). In the late 1980's, PSA testing, which was initially developed for prostate-cancer surveillance, was rapidly and widely adopted for screening of asymptomatic men. The widespread use of PSA testing was based on its increased detection of early-stage cancer as compared with the digital rectal exam (DRE). Screening and diagnosis rates increased about 2% per year, reaching a peak in 1992. Treatment rates are also known to have peaked at this date, though there was substantial geographic variation in practice. The first PSA guidelines were also released in 1992, at the peak year of screening, before the first results from Randomized Controlled Trials (RCT's) became available. In 1995, *The Gray Sheet*, a weekly newsletter that covers the medical device and diagnostic industries, said that device manufacturers had little incentive to seek FDA approval of their PSA tests, and that 90% of tests were off-label (The Gray Sheet, 1995).

The first RCT results came only in 1999 after the PSA test had already been diffused in the U.S. population. By 2001, a population-based survey in the U.S. showed that about 50% of at-risk men had had a routine PSA test and 75% of men over 50 years had previously had a PSA test (Sirovich, Schwartz and Woloshin, 2003). Figure 2 shows the frequency of first PSA tests and repeat tests in the U.S. population (Mariotto, 2007): frequencies are for men aged 50–84 years. Important milestone events are added to this timeline. Jemal et al. (2015) found that after the 2012 USPSTF recommendations both the rates of PSA screening and incidence of early stage prostate cancer have declined moderately.
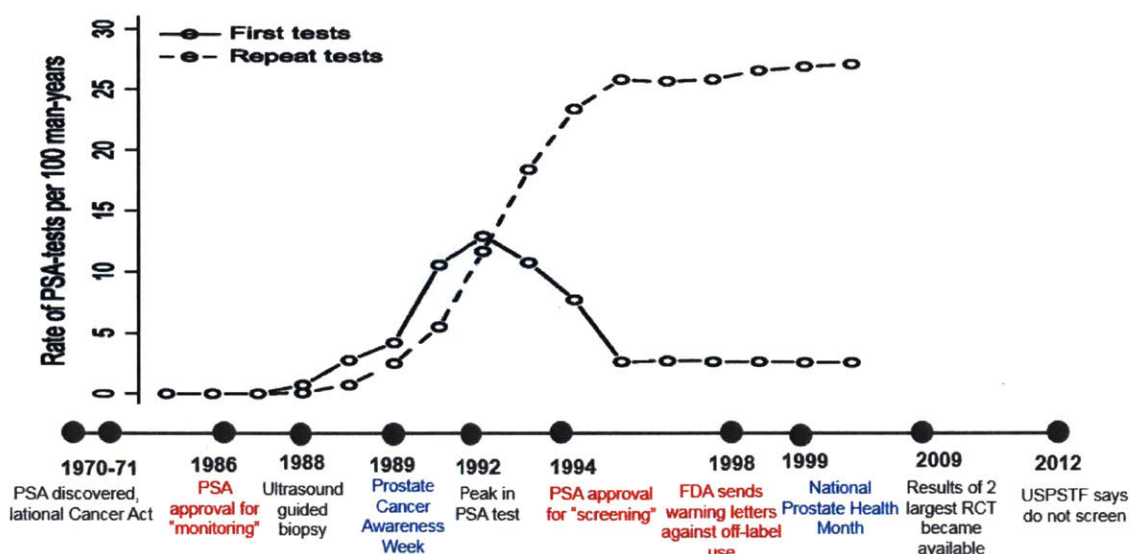
Figure 3 Dissemination of PSA screening practice in the U.S.; I added events to timeline

Disease Awareness: All these changes in screening dissemination and disease incidence happened during an era where screening was usually being promoted in the U.S. and internationally. For example, the Prostate Cancer Awareness Week was established in 1989, and the first National Prostate Health Month (Prostate Cancer Awareness Month) was launched in 1999. I summarize other important disease awareness events in Table 2.

Table 2 Major Disease Awareness Events

1987	*Men's Health* magazine launched in the U.S.	Known as the best-selling men's magazine on US newsstands.
1987	National Cancer Survivors day was announced in Albuquerque	The day is mainly observed in the US
1989	Prostate Cancer Awareness Week is launched	The week of September 17 to September 24, primary purpose is the education of the public and promotion of early detection of the disease.
1982	Men's Health Network is established in the U.S.	MHN has presence in every state, over 30 countries. MHN conducts screenings in the workplace, promotes other awareness events such as the Men's Health Month, Men's Health Week
1992	US Senator Bob Dole publicly revealed that his life was saved by the PSA test	
1994	Men's Health Forum founded in the U.K.	About 12 years after the U.S.
1999	September is designated as the National Prostate Health Month	Launched by the American Foundation for Urological Disease (AFUD), now known as the Urology Care Foundation.
1999	The US Postal Service issued a stamp advocating annual PSA tests	

21

2000	Toronto Men's Health Network founded in Canada	About 6 years after the U.K., 18 years after the U.S.
2000	Senate Resolution 138 endorsed Prostate Cancer Awareness month	Prostate Cancer Awareness month's annual observance is affirmed
2002	International Men's Health Week began at an international level in 2002	Announced when six men's health organizations around the world met in a meeting organized by MHN at the 2nd World Congress on Men's Health
2003	In a 2003 presidential proclamation, President George W. Bush voiced his support for Prostate Cancer Awareness Month	The month of September is specifically named as the "National Prostate Cancer Awareness Month."
2009	Kimberly Clark Corporation's Depend brand launched "The Depend Campaign to End Prostate Cancer"	Kimberly Clark mainly produces paper products, and Depend is the male-incontinence product line for PCa treatment harm reduction, leading brand with 30% market share
2012	American Urological Association (AUA) started "Know Your Stats" National Prostate Cancer Awareness Campaign	The 4th annual campaign, partnered with other groups, e.g. with National Football League

Landmark Publications: In 1987 urologist Dr. Thomas Stamey published a landmark paper in *The New England Journal of Medicine* showing a correlation between increased PSA levels and prostate cancer (Stamey et al., 1987). Two years after this publication, in 1989, FDA approved the PSA as a "follow-up, or surveillance" test for men who already have prostate cancer, yet the test was known to be widely used as an off-label tool also for asymptomatic men after this date. Around the same time, early autopsy studies revealed a high prevalence of "clinically silent" cancer (Carter et al., 1990)

One of the other prominent figures of the PSA debate, urologist Dr. William Catalona, published results of a study in 1994 that was used to support the FDA approval of the PSA test for asymptomatic men (Catalona et al., 1994). The study showed that the PSA test, in conjunction with the digital rectal exam (DRE) increased the cancer detection rate from 3.2% for DRE alone to 5.8% when the two methods were combined, with a biopsy threshold of 4 ng/ml. A few years later, another study showed that of those men who had a PSA test result between 2.6 and 4 ng/ml, 22% of them also had prostate cancer (Catalona et al., 2000). Based on this finding Dr. Catalona advocated to lower the clinical threshold to 2.6 ng/ml, "to enhance detection of curable prostate cancer." Similarly, a study published in *The New England Journal of Medicine* showed that some fraction of men with PSA values less than 4 ng/ml might also have prostate cancer, or that "a normal PSA value does not rule out prostate cancer" (Thompson et al., 2004).

Fifteen years after this initial publication, Dr. Stamey changed his stance on the usefulness of the PSA test, indicating that serum PSA was related to prostate cancer 20 years ago, but in the last 5 years serum PSA had only been related to benign prostatic hyperplasia (BPH). The paper suggests that "The PSA era is over in the U.S." (Stamey et al., 2004). A year later, Dr. Catalona responded with a paper published in *European Urology*, suggesting that "The PSA era is not over for Prostate Cancer" (Catalona and Loeb, 2005).

The long-awaited first results from Randomized Controlled Trials (RCT) of the use of PSA testing came only in 1999, after the complete diffusion of the PSA test in the U.S. Unfortunately their results were conflicting and added to the existing controversy on the efficiency and extent of use for the test. The European Randomized Study of Screening for Prostate Cancer (ERSPC) trial showed some moderate mortality benefit, where 1 death was averted when 1410 men were screened for 9 years, and when 48 cases were treated for prostate cancer. Yet the North American Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial showed no mortality benefit after 7 years of follow-up (Schroder et al., 2009; Andriole et al., 2009). This finding led USPSTF to recommend against PSA screening in 2012. The former chief medical officer for the American Cancer Society, Otis Brawley, also changed his stance on PSA screening in 2012 (Brawley and Goldberg, 2012).

Today, PSA level is used in combination with other biomarkers to stratify patients into their respective risk groups, yet there is still no perfect way to predict which tumors will cause clinically important illness. Consequently, the majority of men in the US with an early-stage cancer opt for a treatment (Cooperberg et al., 2010). Some professional societies recommend selective testing (Wilt and Ahmed, 2013). Other important landmark publications are listed in online Appendix (PSA Timeline.xlsx).

Evidence for Selection Criteria in PSA Screening

PSA selection criteria include the recommended initiation and stopping ages of PSA screening, and the cutoff PSA level for biopsy referral. The age thresholds differ for asymptomatic/normal risk versus high-risk men, the latter being on average five years lower than the former. In this paper I are consider the PSA test for screening of healthy, asymptomatic men at normal risk.

Variation in Policy Decision Threshold of Starting (and Stopping) Age to Screen: Figure 4, Figure 5 and Table 3 summarize the empirical data collection for the recommended starting ages of most commonly used prostate cancer screening guidelines developed in the United States: 1- US Preventive Services Task Force (USPSTF), 2-American Cancer Society (ACS), 3-American Urological Association (AUA), and 4- National Comprehensive Cancer Network (NCCN). Extended results for most national and international guideline-issuing organizations are documented in the PSA Timeline at online documentation.

Literature search results confirm some fluctuation in previously suggested PSA screening thresholds, particularly in the American Urological Association (AUA), and the National Comprehensive Cancer Network (NCCN) guidelines, which are the guidelines most highly regarded by medical specialty groups.

Figure 4 Data collected for Recommended PSA starting age for asymptomatic men, by professional organization

Figure 5 Summary of Major PSA Guidelines for 4 major professional organizations (BIGGER VERSION ON APPENDIX B)

Table 3 Summary of four practice guidelines with regard to recommended starting age for PSA screening

ACS issued updates in 1992, 1997, 2001, 2006, 2010, and 2014	
1992	PSA test recommended starting age is 50.
2010	Individual Decision Making (IDM) is suggested for men over 50, relaxing the threshold for age of initiation, while the biopsy threshold is decreased to 2.5 ng/ml (previously 4 ng/ml)
2014	IDM for men over 50, biopsy threshold stays the same
AUA issued updates in 1992, 2000, 2009, and 2013	
1992	Recommended starting age is 40, biopsy threshold of 4 ng/ml
2000	Recommended starting age is increased to 50 (men>50)
2009	Recommended starting age is decreased to 40 (men>40)
2013	Recommendation increased to 55, biopsy threshold increased to 10 ng/ml for men>70.

NCCN issued updates, in 2002, 2003, 2004, 2010, 2011, 2012, and 2014	
2002	Recommended starting age is 40, frequent follow up for men with PSA 2-4 ng/ml
2003	Recommendation increased to 50 (men>50), frequent follow up for men with PSA 2-4 ng/ml
2010	Same age, biopsy referral threshold is decreased to 1 ng/ml
2011	Recommended starting age is decreased to 45
USPSTF issued updates, in 2008 and 2010	
2008	Evidence incomplete for men under 75; men over 75 should not be screened.
2012	Discontinue use of PSA test for men of all ages

The U.S. Preventive Services Task Force (USPSTF) is a government-appointed expert panel whose stance influences coverage of screening tests by Medicare and many insurance companies. In 2012, USPSTF issued a draft recommendation against PSA screening for asymptomatic men, regardless of their age, racial or ethnic group, or family history. The task force concluded that the harms of screening outweigh the benefits. Previously, in 2008, before the two RCT results came out, they said evidence was incomplete to make a judgement for men under 75, but men over 75 should not get screening.

Before 2009, recommended starting ages for asymptomatic men were 50 for ACS, 40 for AUA until 2000, and 40 for NCCN until 2003. Both AUA and NCCN increased their policy thresholds to 50 after these dates. In the absence of results from controlled trials, these policy thresholds were based on systematic reviews of the literature, or expert panel opinions, and a consensus-building process. USPSTF recommendations in 2008 were drew on findings of a commissioned systematic review and harms-and-benefits simulation modeling (Pignone and Sox, 2008), which separated the systematic review process from that of guideline development (Imperiale and Ransohoff, 2010).

It is important to note that most policy decision thresholds were changed after 2009, but not all changes were in the same direction. USPSTF issued a draft recommendation against screening for all ages in 2012, while the NCCN decided to decrease its age threshold from 50 to 40 in 2010, and the AUA decreased it to 40 in 2009. Only three years later, in 2013, the AUA increased its age threshold to 55, and at the same time also increased its biopsy threshold from 4 to 10 ng/ml for men over 70. Throughout these years ACS recommendations stayed constant at 50 yet after 2010 they didn't directly recommend screening for men over 50, but suggested that a Shared Decision Making (SDM) discussion take place between the patient and provider. To date, professional societies still vary in their advice. Medicare provides coverage for annual PSA testing for Medicare-eligible men over 50, and private insurers continue to provide coverage for the test.

Decision Threshold for Biopsy Referral: The optimal limit of the normal range of a total PSA test is not yet established, but it has long been known that benign enlargement of the prostate (benign prostatic hyperplasia, or BPH) causes PSA to rise as a natural consequence of aging. A man's PSA level can also rise with prostatitis, urinary tract infection, biopsies, surgery, or with some drugs. The continuous nature of the total PSA distribution is demonstrated with a histogram in Figure 6, which shows two waves of NHANES data for US men 40 years and older who have not had a diagnosis of prostate cancer previously (NHANES 2001-2002 and 2007-2008).

In the US the most commonly used formal criterion for biopsy referral is 4 ng/ml (Cooner et al., 1990, US PLCO trial). This cutoff suggests a high sensitivity yet a lower specificity with a 50-60% false positive rate (FPR), 15% false negative rate (FNR) and a 30% overall positive predictive value (PPV) (Hoffman, 2011). Another complication about the threshold is that studies to establish the normal levels have been conducted predominantly for white men and may not reflect racial differences.

The actual biopsy threshold also has varied widely over the years (Thompson et al., 2004), as has the recommended starting age. Values as low as 2.5 ng/ml, and as high as 10 ng/ml were suggested as the upper normal limit (Seamonds, 1986; Kuriyama, 1980; Yang, 1984; Liedtke, 1984 for 2.6 ng/ml; Catalona et al., 2000; Labrie et al., 1999; Krumholtz et al., 2002; ACS, 2014 for 2.5 ng/ml; Kuriyama, 1982; Pontes, 1982 for 7.5-10 ng/ml). The European Trial (ERSPC) used a cutoff value of 3 ng/ml (Schroder et al., 2009) and more recently the 2013 AUA guidelines proposed 10 ng/ml as the upper limit for men over 70 (Carter et al., 2013). Age-specific ranges have also been proposed, as PSA is known to increase by age (Catalona, 1997).

Another suggestion was to use the other components of the total PSA to suggest additional thresholds to improve the low specificity of the test, such as using the Percent Free PSA (Luderer et al., 1995); PSA Density (total PSA level divided by the prostate volume, Benson et al., 1992), or the PSA velocity (the rate of change in total PSA over time, Carter et al., 1992). Most recently, a metric called the Prostate Health Index (PHI) has been suggested that combines all three forms into a single score (Catalona et al., 2011). In addition to these PSA-derived metrics, numerous other biomarkers have been proposed to improve the diagnostic accuracy of the test, but their clinical usefulness remains unclear (Prensner et al., 2012; Crawford et al., 2014, Huang et al., 2014).

Variation in Policy Decision Threshold for Biopsy Referral: I gathered data from several sources for the biopsy threshold of the PSA test. Figure 7 presents suggested biopsy criteria for four major guideline issuing organizations in the US.

The USPSTF issued two position statements on the use of the PSA test, in 2008 and 2010, yet no biopsy referral threshold was indicated in these statements. ACS issued six updates in 1992, 1997, 2001, 2006, 2010, and 2014. From 1992 to 2014 the threshold was 4 ng/ml, and after 2010 ACS suggested Individual Decision Making (IDM) for men with a PSA result higher than 2.5 ng/ml. AUA issued four updates in 1992, 2000, 2009, and 2013. Their cutoff stayed stable at 4 ng/ml between 1992 and 2013, and then, making a drastic change from their 2013 guideline, this threshold was increased to 10 ng/ml (for men above 70 years old). NCCN issued seven updates in 2002, 2003, 2004, 2010, 2011, 2012, and 2014, respectively. Between 2002 and 2010 they recommended frequent follow-up for men with PSA 2-4 ng/ml, and in 2010 the threshold was lowered to 1 ng/ml.

PSA Histogram
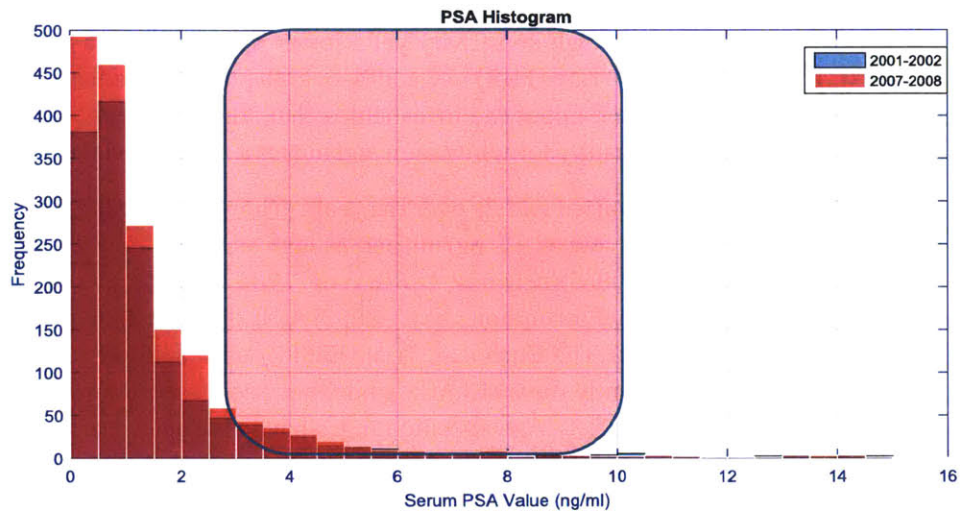
Figure 6 Total PSA Distribution Data: NHANES 2001-2002, and 2007-2008 (data for 5 waves available, 2012-4-6-8-10)

Recommended "formal" biopsy thresholds are shown to vary modestly over time, yet the variation is less than the one in the starting age criteria which is shown to vary since the 1990's (See data in Figures 4 and 7). These formal "policy" thresholds stayed constant at 4 ng/ml throughout the years of screening dissemination; however, the informal "practice" threshold has reportedly been lower than the formal one, suggesting poor compliance with recommendations. The real pattern for the average biopsy threshold is unknown, but it is generally accepted to be 2.5 ng/ml between 1990 and 2000 (Gulati et al., 2010). Also, Pinsky et al (2005) have shown that biopsy frequencies of men with PSA's between 2.5 and 4 ng/ml were at the same order of magnitude as for men with a PSA higher than 4 ng/ml.
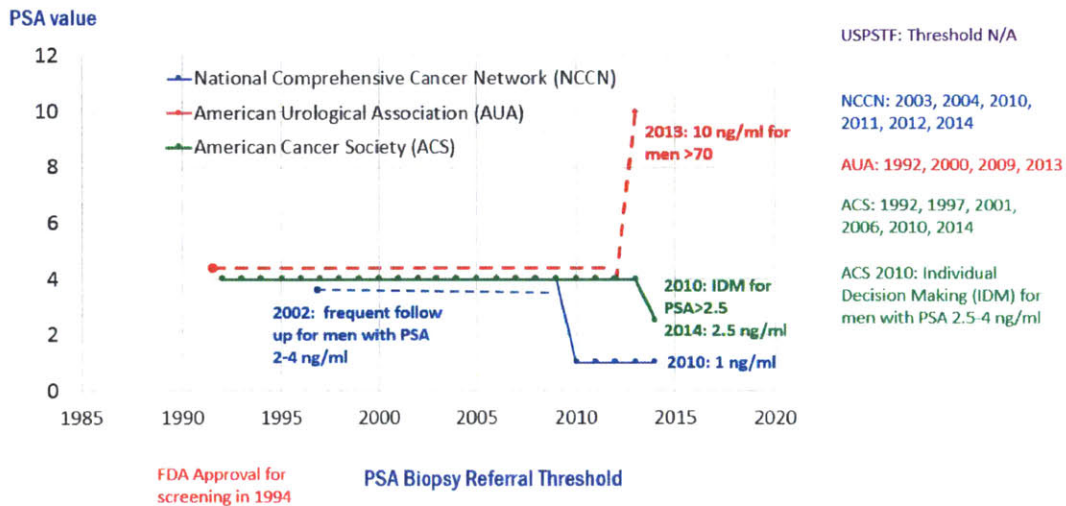
Figure 7 Data collected for PSA Biopsy Referral Threshold, by Professional Organization

27

Expert Opinion Interviews

Participants and Settings: Forrester (1994) regards the "mental database" as the most important information source for the modeler. In order to collect important pieces of qualitative evidence from the PSA screening mental database, I conducted an expert qualitative opinion interview study involving in-depth, semi-structured interviews. This is a purposive sample of 34 health and medical professionals, including clinicians, policy makers from the American Cancer Society, American Urological Association, and the U.S. Preventive Services Task Force; academics and Cancer Intervention and Surveillance Modeling Network (CISNET) group members; advocacy and activist group members; cancer patients; and media reporter/science writers who publish on cancer screening-related issues in various outlets, including *Science*, the *New York Times*, the *Washington Post*, and the *Guardian*. An initial recruitment email, and a semi-structured interview outline were developed to investigate the trends in screening for prostate and breast cancer in the U.S., including the roles of evidence, translation, and risk communication (Appendix D and Appendix E). The main focus was to understand the different sources of variation in screening guidelines and actual practice, and to gather different expert opinion perspectives regarding the PSA screening decision.

Initial invitations were sent in January 2015, after securing consent from the Committee on the Use of Humans as Experimental Subjects (COUHES) at MIT.[1] Interviews took place between January and September 2015. I used the "snowball" method, in which I asked each interviewee who else I should talk to, and continued until getting to the point of diminishing returns on new ideas, and having covered all the major groups of participants. Interviewees had some expertise or experience related to PSA screening for prostate cancer, or mammography for breast cancer, or had an opinion about both, as in the case of media/ science reporters, or primary care physicians. Roughly half of the clinicians were from specialty groups (medical urologist, breast surgeon, etc.), and half were primary care physicians or others who prescribe screening and had an opinion about practice guidelines. I collected data from a total of 34 interviews and were able to obtain informed consent to use 33 of them for the study. One interviewee declined to give consent to use the collected data.

Figure 8 shows the final composition of participants, categorized under 5 major headings: Policy maker, Clinician, Academic, Patient, Media/Science Reporter/Advocacy Group Member. Most participants were active in multiple domains (e.g., academic and clinician; policy expert and academic; advocacy group member and patient; in the case of more than two roles, I picked the most relevant two categories).

Please note that the numbers below do not add up to 33 due to some overlap between the categories, reflecting the fact that most of the participants tend to wear multiple hats in influencing the screening decision. Figure 8 shows that half of the clinicians interviewed had an academic title, and half of the academics were playing a major policy role in influencing the development of clinical practice guidelines. There was also a noticeable overlap between clinician and policy maker categories.

While the first major area of overlap was between policy maker-clinician-academics, the second major area of overlap appears to be between patients and patient advocacy groups. Two out of five

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[1] Committee on the Use of Humans as Experimental Subjects (COUHES) Protocol # 1412006813 Study Title: Dynamics of Routine Screening

media writer/advocacy group members were cancer survivors themselves and others had some opinion on advocacy groups, suggesting close ties between patients and patient advocacy groups. These two patients' membership in advocacy groups was initiated or influenced greatly by their own experience. The primary role of one of the participants (Professor John Barry, Professor in Urology at OHSU, former president of the American Urological Association (AUA) and the American Board of Urology) was being a clinician and policy maker, but as a former prostate cancer patient and clinician he also wrote a book based on his own experience. One participant (Peggy Orenstein, journalist at the *New York Times*) had a primary role as a media/ science reporter, but also had an interesting experience as a breast cancer patient herself which—as she said—influenced her greatly to write on these issues to inform the general public.

Figure 9 shows the composition of 33 interviewees based on their primary roles. The distribution of categories between clinicians, academics, and policy makers were almost the same with 16, 14, and 12 interviews, respectively, while the second most common participant title was the advocacy group/ media/ science reporter, with eight interviews in this category. I had fewer interviews with patients, comprising 15% of all interview data (five patients in total; three of them had a different primary role and hence were categorized elsewhere).
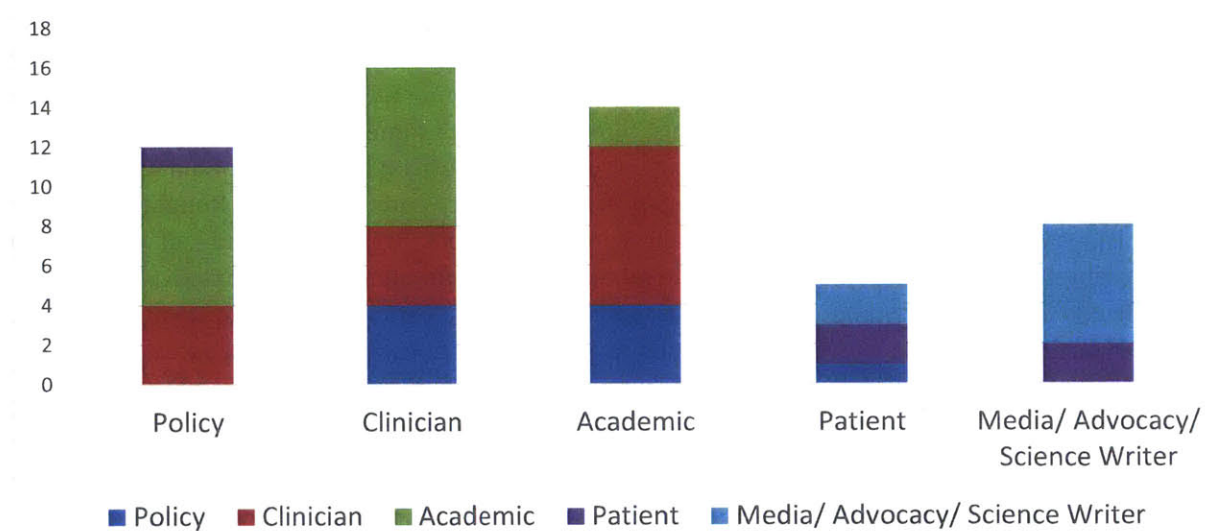
Figure 8 Interviews Composition

Interviews were conducted by the author, by phone and in person when it was possible. They ranged in duration from 20 min to 2 h and 35 minutes. All interviews were audio-recorded, de-identified and transcribed verbatim. Participants were not compensated for their time.

Interviews were semi-structured, and the interview outline varied according to the particular knowledge of the interviewee, as modified for different categories of participants (medical and health professionals, media and advocacy groups, patients). The main outline can be seen in Appendix E. The interview schedule covered a broad range of topics, and was modified between interviews, informed by the developing analysis.

Total = 33 interviews, by main title

- Academic
- Clinician
- Policy
- Patient
- Media/Advocacy/ Science Writer

16%
23%
9%
25%
27%
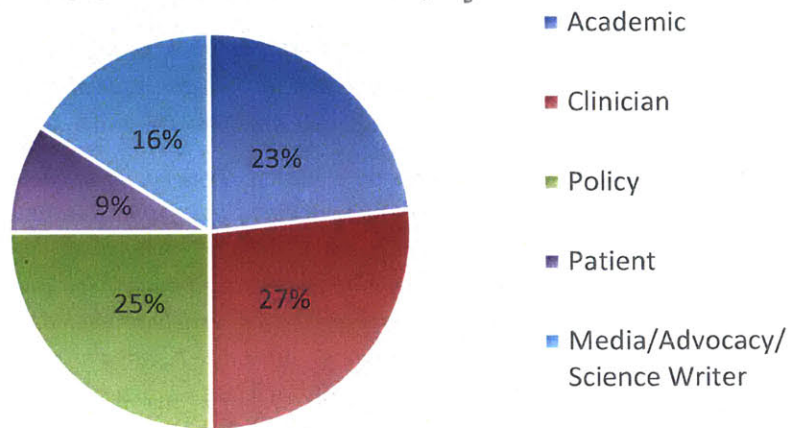
Figure 9 Interviews Composition (IF THEIR PRIMARY TITLE IS USED)

Data coding and analysis: Using the collected interview data, I undertook a formal thematic qualitative analysis as it related to drivers and determinants of screening. Data analysis was conducted using grounded theory techniques and system dynamics field-specific research on how to use qualitative data (Glaser and Strauss, 1967; Burchill and Fine, 1997; Luna-Reyes and Anderson, 2003). First, I developed an initial analytic framework from the identification of the key issues within the interview outline and the data. This initial coding framework was then used to analyze the interview data, with themes added as new issues emerged in subsequent stages. Data across the whole set as well as within each individual interview were examined under nine major headings, and 69 minor headings, with over 2400 coded segments. A free qualitative software package, MaxQDa, was used to facilitate management of the collected data. Major headings in the Coding System are the following: I- Guidelines, II- Screening, III- Treatment, IV- Main Issues Mentioned, V-Interviewee, VI-Patient, VII-Policy Thresholds, VIII- Cognitive Factors and IX-Feedback.

Key Behavior Modes/ Core Reference Modes

Fluctuations in Screening Thresholds of Clinical Practice Guidelines

The first reference behavior mode that I observed on data are persistent fluctuations in CPG's of various guideline-issuing organizations, and especially in specialty groups. Since PSA testing was widely adopted before its benefits and harms were formally established in randomized studies, these fluctuations are hard to explain by corresponding objective changes in the benefits-and-harms environment. They are also hard to explain by other technologies that would motivate a legitimate change in the screening guidelines, or by events in the environment which would make screening guideline changes rational. The results from randomized studies also seem not to have reduced existing fluctuations and led to convergence on stable guidelines. Instead, these results were followed by both expansion and contraction in decision thresholds of screening after 2009 for the specialty groups. The fluctuations in screening indications and the role of the scientific evidence base were

30

among the emerging themes in the interviews. Participants in general mentioned and criticized the "pendulum" in screening, which is now recognized as a potential problem by the scientific community (Penson, 2015):

"We've taught the public that screening is so important and so vital, and you have to detect cancer at the earliest possible stage, and now we're backpedaling, and people don't like that!" —Deborah Kotz, Press Officer at FDA

"I know less about PSA screening. My impression is that the evidence of the benefit of PSA screening is less than for mammography, but with mammography, which I have studied a bit more, I think-- it's clear that there are risks associated with just broadly advocating mammography. So there's been sort of a national pendulum in the general public viewpoint. In the beginning, people were all gung ho for it. Everybody thought it would be great, so it was widely used and widely promoted, but then after a period of time, you begin to see that there are flaws and problems, and those begin to create a backlash, or criticism, and I think you need to report both of those..." — Media, Science Reporter

Interview participants generally agreed that screening should be guided by scientific evidence in an ideal world, but almost none of them claimed that screening in actual practice is determined purely by the available clinical evidence of benefits and harms. The other determinants they mentioned and the importance that they assigned to them varied widely, but common themes listed were the social, cognitive, and political factors around the screening decision, including risk perception and fear, industry, and other elements of bounded rationality:

"So, in my opinion, that's why determinants [of screening] are, again, evidence, and the cost issues, but then I think there are non-quantitative, non-mathematical, - I would say nonscientific issues coming into play..." — Oguzhan Alagoz, Professor, Industrial and Systems Engineering, University of Wisconsin-Madison, Cancer Intervention and Surveillance Modeling Network (CISNET)

"It's an interesting piece that you're doing, because it's not just a matter of looking at the evidence and saying it's appropriate or not. We've taught the public that screening is so important and so vital, and you have to detect cancer at the earliest possible stage, and now we're backpedaling, and people don't like that! They don't like when we tell them one thing, and then ten years later, tell them, "You know what? Maybe we've oversold screening in this country. Maybe we've oversold it a little bit. Maybe you don't need it." So I think that that's angered a lot of consumers." —Deborah Kotz, Press Officer at FDA

"I think that's very interesting, because if you look at the [scientific] evidence, it [screening vs. not screening] doesn't really make a big difference, so it must be something else then, let's say, the medical effect. It's culture, it must be something else, that defines what you recommend and what you do not recommend, and I think that's really interesting." — Clinician, Academic

Over-screening and Over-diagnosis

The second reference mode that I observed on data is over or under-screening that is not seen in just one therapeutic category, one disease category, but emerges as a generic phenomenon across most

disease categories. It is difficult to know if over-screening has occurred in an individual, but it is relatively easier to know if it has occurred in a population.

There are several definitions in the literature, but basically "over-diagnosis" is the diagnosis of a cancer that would otherwise not go on to cause symptoms or death. In other words, an over-diagnosed case is an excess case detected, or caused, by screening. It is difficult to know if over-screening or under-screening has occurred in an individual, but it is relatively easier to know if it has occurred in a population.

It is well known that the majority of prostate cancer cases are latent and remain undiagnosed in the absence of screening (Carter et al., 1990; Etzioni et al., 1998; Draisma et al., 2009; Jahn et al., 2014), and a large proportion of PSA-detected prostate cancers are considered to be over-diagnosed. There are two prerequisites for cancer over-diagnosis to occur: The existence of a silent disease reservoir, and activities leading to its detection, such as (over)screening (Welch, 2011). Finding an otherwise non-progressive cancer is not harmful by itself, but there is no way of distinguishing an indolent or latent cancer from one that is likely to progress.

Knowledge of the likelihood that a screen-detected case of cancer has been over-diagnosed is important to develop a sound screening policy and inform clinical practice. However, estimates of the frequency of over-diagnosis in cancer screening vary greatly across studies (Etzioni et al., 2013). Estimates of prostate cancer over-diagnosis range from 23% (Telesca et al., 2008) to 66% of PSA-detected cancers, which would not otherwise be found without screening (Pashayan et al., 2006; Hoffman, 2011). A study has estimated that 1 million additional men have been diagnosed and treated for prostate cancer after the introduction of PSA screening; however, the decline in the mortality rate observed during the same period is not of the same order of magnitude (Welch and Albertsen, 2009).

Over-diagnosis due to large pool of indolent (latent) disease: One aspect that increases the reported prevalence is the existence of a silent pool of indolent disease, which varies among different types of cancers. These are "true-positive" cases where the disease identified has uncertain significance, and where men would never become aware of their disease if they were not tested for it, as evidenced by the silent reservoirs of undetected thyroid, (Harach et al., 1985), breast (Nielsen et al., 1987) and prostate (Montie et al., 1989; Jahn et al., 2015) cancers. The most recent study by Jahn et al. (2015) combines autopsy results for men who died of other causes to indicate the size of this indolent pool of prostate cancer (see Figure 10).

Controversy of Over-screening and Over-diagnosis: The rationale for routine screening is that early detection and treatment of asymptomatic cancers extends life, as compared with treatment after clinical diagnosis. Effective cancer screening has two requirements: 1- The screening test has to detect clinically relevant cancers at a preclinical stage; and 2- Available treatment options should result in improved outcomes when administered early, rather than after the clinical diagnosis. These two conditions should hold at the same time for screening to be effective: Cancer should be detected at an earlier stage, and should then also be more easily treatable when compared to previous practice, leading to less mortality and less morbidity on a population basis.
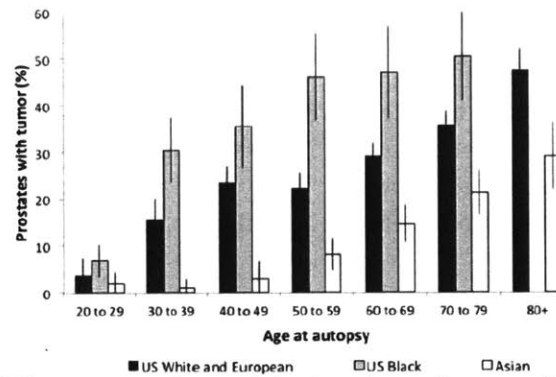
Figure 10 Prostate cancer diagnosed at autopsy by age, Summary of 19 studies

The notion that early detection works was the main overarching theme that was mentioned by most supporters of screening, reflecting this as a major paradigm that drives screening dynamics in the U.S. Opinions about the importance of early detection and the degree to which it benefits or harms the patient varied widely between participants and subspecialties of clinicians. Most of the participants acknowledged that they might have their own bias on this issue because of their past experience and observations, and some of them referred us to other groups and people so that I could get a different perspective. Two main categories quickly emerged—supporters of screening versus agnostics—while some maintained a more in-between impartial position.

The issue of the existence and degree of over-screening and over-diagnosis also emerged as the most controversial theme in the interviews. Participants usually had some acknowledged biases for themselves and for others. One school of thought (mostly including academics and some policy makers) generally argued that the paradigm of early detection led to many diagnosed cases and unnecessary procedures, while another school of thought (mostly including clinicians and advocacy group members) mentioned the effect of early detection in reducing the morbidity from the disease, if not the mortality *per se*.

One very interesting observation was that participants' lists of perceived harms and benefits of screening varied widely, and included different elements based on their position and perspective on the issue of over-diagnosis. Screening proponents argued for the benefits of early detection, while the other group was less convinced about the benefits and more concerned about potential harms. (APPENDIX J- Perceived Harms and Benefits Environment). Here are some illustrative quotations:

"If you take enough time to understand what this means, if I tell a patient, "Look I'm 47, my probability to have a prostate cancer histologically under the microscope right now as I sit here, is about 30%. Period." That's a start, so there's a pool of prostate cancer that we all carry, most of them they'll never become symptomatic, some of us have to have bad cards. Do we understand who have bad cards and who don't? No, we don't. There's a residual risk that there's something going on…. But what I can also tell you, if you get into this entire diagnostic work or the therapeutic work of what the consequences are at that time, and then we discuss that and patients understand these aspects, that's fine. You can also make a patient understand what an over-diagnosis indeed is." —Peter Juni, MD-PhD, Director, Applied Health Research Centre, St. Michael's Hospital, and Professor of Medicine, University of Toronto. Previous: Director of the Institute of Primary Health Care, Switzerland

33

"PSA is overused because first no one wants to be blamed to miss a possible prostate cancer diagnosis and second most of the patients ask for it. Additionally, we also know that PSA is not specific for prostate cancer and it can be increased in other prostatic diseases such as benign prostate hyperplasia or prostatitis." — Ilker Tinay, MD, Urology, Marmara University School of Medicine, Formerly: Brigham and Women's Hospital, Urology

"The most important harms are really over-diagnosis and over-treatment. Those are basically the most important ones. To get a good schedule on that is crucial." —Harry de Koning, Professor of Evaluation of Screening, Biochemistry and Pharmacology, CISNET modeling group

"Yes, there was too much uncritical use of screening early on, maybe in the 70's, and it was kind of a national movement led by some people who thought this was just a great cause, and everybody should get screened, and gradually more critical thinking came in and they tried to define who was most at risk. If you want to ask some specific questions, I think PSA and mammography screening, it has been overused. I think, gosh, I don't know if it was ever underused, because it wasn't that much available in the beginning, but certainly it's everywhere now I think. So I don't think it's underused..."—Media, Science Reporter

"It's a general question for things that will vary by regions and by practice, and by opinion. It's almost impossible to answer. You only know in retrospect if you made the right decision. In other words, if a 70-year-old man who otherwise appears fit has a series of prostate biopsies, becomes septic and dies from sepsis in the hospital, well, you made a mistake. If an otherwise healthy patient who is in his mid-60s has a radical prostatectomy, is discharged from the hospital, goes home, has a DVT and a pulmonary embolism and dies, you made a mistake in treatment. Some people shouldn't have married their first spouses; you only know in retrospect that it was a mistake." —John D. Barry, Professor of Urology and Professor of Surgery, Oregon Health and Science University, former chair of AUA

A related notion that emerged from the interviews was the difficulty of conveying the idea of over-diagnosis. "It is very hard to challenge a paradigm, and it is not intuitive." Some participants said that over-diagnosis is a very hard concept to grasp, and some clinicians complained about the difficulties of explaining the guidelines, or the probability of over-diagnosis, to their patients. Clinicians also, interestingly, said that as a clinician or as a policymaker, they would behave very differently, as "things are more difficult when you have a real patient in front of you." There was general agreement that the PSA test is less efficient than mammography, or at least that was the perception because "overtreatment is more obvious in the case of PSA and hence easier to prove." In other words, while benefits of cancer screening are obvious (avoiding a death from cancer), harms were more subtle and difficult to communicate even to most educated people.

"Barbara [Brenner, former president of Breast Cancer Action] was really the person who started saying to me, "You've got to look at the screening thing, you've got to look at the screening thing, you've got to look at the screening thing," and she would explain to me what the issue was and I kind of couldn't grasp it. I kept saying, "It's got to be better to find it earlier," she's like, "Well sometimes, sometimes not," and it took me really a long time to wrap my mind around what....it doesn't make sense....It just was so hard to understand it. The same thing happened to me when I wrote my article. I kept trying to explain it to my editor and she kept saying, "Yes, but..." and I go, "Well no, because of this, this and this." I felt like if I could get it across to her and then when I finally got it to her it got bumped up to the next editor up, who

weeds everything. There were two top editors who read everything in the magazine. Then she said, "Yes, but this doesn't make any sense..." —Peggy Orenstein, Journalist, NYTimes

APPENDIX M summarizes the interview data for perceived sources of biases in the screening decision, and Appendix N lists the sources of non-compliance with practice guidelines.

Elements of Bounded Rationality in the Screening Decision

In the context of screening, bounded rationality may imply the presence of selective information, misperception of risk, time constraints in decision-making for screening and possible treatment options, time constraints in waiting for evidence to be published, and delays in changing and adjusting to standards for screening. Selective information may include, but is not restricted to, the visibility of cancer survivors, anecdotes from survivors or relatives, or (for clinicians) the specialty effect. Research shows that these contribute to the public's, clinicians' and policy-makers' tendency to misperceive risks and incorrectly assess the potential consequences of their actions.

In line with prospect theory, where people respond more to options that are described as losses rather than (equivalent) gains, people have been shown to be more likely to obtain a screening test if the costs associated with not getting the test are emphasized, rather than the benefits of getting it (Edwards, 2001). It has been further shown that anecdotal messages have more impact than statistical messages, and that positive anecdotes (about gains from screening) are less persuasive than negative anecdotes (about the losses from failing to get screened).

Below I present evidence from the expert opinion interviews for elements of [some of it is self-perceived] bounded rationality in screening decision. APPENDIX F and APPENDIX G list a summary of data for bounded rationality in screening decisions, and the public's risk perception.

(Mis) Perception of Risk

Recent research shows the importance of risk communication and literacy in medical decision making (Opreskalski and Barbey, 2016; Fischoff and David, 2014; Woloshin et al., 1999). The way the risk information is displayed, or "framed," can substantially affect the perceived risk, and past information has an effect on the perception of new risk domains.

Slovic et al. (1982) identifies two dimensions of risk as dread and fatality, and in later research he shows the most "dreadful" five conditions for women to be Alzheimer's disease, stroke, breast cancer, blindness, and heart disease. The expert interviews also suggest that cancer is a very feared disease— a "dread disease" for both men and women:

"People are very nervous of breast cancer. If you ask women what they die of it's not cardiovascular disease, they think they die of breast cancer. It's the scariest thing out there for women. I think that some of that is obviously mammograms and getting back these reports that are worrisome, but a lot of it's just what they're hearing."—Clinician

"It's, I mean, for an individual, they might say it doesn't matter to me. I just want to be safe. I don't care if it's unnecessary. I don't want the risk. I don't want to live with that risk....And people have trouble

understanding just how big the risk is. I think any mention of cancer is scary, very scary..."—Media/ Science Reporter

"Fear of cancer. Opinion about the primary care physician. Fear on the part of the patient for treatment side effects. Concern on the part of family and spouse about undetected cancer, untreated cancer, or improperly treated cancer. Healthcare cost, and access to healthcare... For instance if you live in eastern Oregon you're six hours away from a major medical center where you could have a radical prostatectomy." — Policy Maker/Clinician (John Barry, Former President of the American Urological Association and Professor of Urology and Professor of Surgery, Oregon Health and Science University)

"There's no question that fear of cancer is widespread and pervasive. Other people have written about what cancer means culturally, as the dread disease. And that cultural analysis of what cancer and fear of cancer means is an important area of study and thought in its own right. ...I want to be very clear, that I do not think there is a single right answer in terms of how people navigate a cancer diagnosis. Fear is real and I think part of patient-centered healthcare and wellbeing means acknowledging that."—Advocacy Group (Karuna Jaggar, Executive Director, Breast Cancer Action)

"I think the major determinants are, I think, the commerce and industry and the perception of the public. That's not the case in Europe. I think in the U.S., I think these are, let's say, quite important. I believe in evidence. This is my major role and my major career, but I certainly believe in evidence. I think in many instances it is number one, certainly evidence-based, doing trials, doing quantification, and cost-effective itself, so it should be number one, but because you especially asked about how much screening is going on, and I think in the U.S., I think these public perceptions and industry are forcing it to play a major role, I think, yes."—Academic (Harry de Koning, Professor of Evaluation of Screening, CISNET)

"It's really weird when you think about it. Women are, they've been made very, very afraid of breast cancer. Way more proportionately afraid of it than they should be. There's this whole idea of misfearing, which is fearing the wrong thing....Women's misfearings. Women ought to be really afraid of heart disease, right? That's what they should be afraid of, that's what's probably going to kill them. But they're super afraid of breast cancer because we've made everybody so damned aware of it with the pink ribbon first of all, and secondly because we've created this whole new class of survivors through mammography, the so-called survivors. So there's a lot of women who have had it all over the place all of a sudden, so it's much more seemingly prevalent, and there was an authentic rise of course of breast cancer in the '70s and '80s and '90s..."—Media/ Science Reporter (Peggy Orenstein, Journalist, NYTimes)

Cancer Survivors/ Feedback Asymmetry in Screening Decision

As of 2014 there were 14.5 million cancer survivors in the U.S., out of which 2.9 million were prostate cancer survivors. This pool is expected to grow to 19 million by 2024 (DeSantis et al., 2014) due to aging, population growth, and improvements in early detection. Today many of us know someone who has received a diagnosis of cancer; it is a diagnosis that is hard to forget, and makes a lasting impression on anyone who hears of it. The "availability" of this mental impression is shown to lead to an enhanced sense of risk. The field of cognitive psychology suggests that it is this "availability heuristic" that leads people to perceive risks as higher than they actually are (Kahneman, 1974):

"We all know cases where people would not have had their disease detected if they hadn't been screened early. It's not necessarily proven that they would not have survived without that screening. We can't know

that for an individual, and studies of many individuals can be misleading because of biases like lead time bias and length bias. What many people respond to, however, are anecdotes. You hear about a women whose breast cancer was detected by mammography in her 30s or 40s, or PSA in a younger man that can seem pretty compelling. And anecdotes are really powerful, in fact we learn a lot from anecdotes and anecdotes are really important. But they're only one small piece of evidence and not usually the most useful piece of evidence. I think anecdotes drive some screening that's not necessarily warranted... "— Matt Gillman, M.D., S.M. Director, Environmental Influences on Child Health Outcomes (ECHO); Office of the Director, National Institutes of Health

"Honestly, that's the problem. It's a combination of factors. I think honestly part of it now is because breast cancer is so common. Everyone knows someone that's been treated, everyone knows someone that's had a recurrence. I think as a society we have less tolerance for inconvenience, and that just evolved over time. So people have the idea, "I just want to get it over with and get it done, and get back to my life." We live in a very, "I want it now," and disposable society. I think that has something to do with it as well."— Deanne Attai, MD, Former President at American Society of Breast Surgeons, Clinical Professor of Surgery UCLA

"So if you look in the mammography trends, screening trends, or if you look at actual cancer incidence, they're different. There's the Betty Ford bump, of when Betty Ford, she was the wife of Gerald Ford. So when she was diagnosed with breast cancer, there seems to be like a little bump in incidence, and I think the same is true for colorectal cancer, when Katie Couric had a colonoscopy on TV, or something, talked about it on TV, because I think her husband died of colorectal cancer..." — Natasha Stout, Professor, Harvard Medical School

While we can easily see people who are diagnosed with cancer after a screening test, we do not as easily see that some of them may be harmed by screening, and may have received unnecessary treatments which wouldn't have changed the result. This is so partly because it takes more time to see the side effects of screening; partly because the victims of screening are not as visible as the survivors; and also partly because—in the absence of the counterfactual—some of these people may incorrectly believe their lives are saved by the treatment. So there is an asymmetry between the immediate positive feedback from cancer survivorship versus the delayed and missing feedback from the invisible "victims" of screening and treatment (Croswell et al., 2010; Ransohoff, 2010). There is also an asymmetry on perceived risks: a negative result from the screening is a non-event, but a positive one is a huge event, which changes the perceived harms and benefits significantly. Woloshin and Schwartz (2010) provide some evidence for this asymmetry in the context of screening decisions for various types of cancer.

"I was like, "What are you talking about? The life that was saved was mine. I am the woman whose life was saved by that under 50 mammogram, and you need to know who I am," so that was why I wrote my first article. [After the USPSTF recommendation to increase the age threshold in 2009]" —Peggy Orenstein, Journalist, NYtimes

"There are two different perspectives: The individual one, and then the sort of public health one, and quite often you will hear people say, "Screening saved my life, so it's worth it for everyone." — Media, Science Reporter

"The treatment we are getting, I cannot judge how good our decision is. I mean, if I had gone with the first option, which is having lumpectomy, I don't know if it would be better or worse. So I mean, it's really difficult to judge, and I don't think either way, either one, is much better than the other one. I think people choose, 50% choose one, the other 50% choose the other option. So I think it mostly depends on your personal choice." —Patient

"So given all of that, the truth of the matter is it probably would not have made a difference, and that's why I say that I probably chose a bigger surgery than necessary." —Patient

There are four possible outcomes after a screening test: If the test result is positive, a biopsy is obtained. The biopsy result may then indicate a malignant (true positive, or TP) or benign (false positive, or FP) condition. If the finding is negative, there is no biopsy. While most men who are not recommended for biopsy do not have malignant mass (true negative, TN), some do (false negative, FN). Each of these outcomes has associated costs and benefits. A TP may mean earlier identification and treatment of cancer, possibly resulting in a better outcome because of decreased morbidity.

The costs of a false negative (FN) include all the costs associated with failure to treat a non-detected tumor. Clinicians understandably want to avoid FN's because undetected and untreated cancer is the worst possible outcome. Because of high uncertainty, avoiding FNs results in many false positives (FPs, or biopsies that turn out to be negative). In the context of PSA screening, the benefits of a TP include the health benefits of a potential early detection and treatment, avoiding a potential prostate cancer death. Benefits of a TN would be the psychological benefits of a correct disease-free diagnosis. The costs of getting a FP include receiving an unnecessary needle biopsy, which may lead to some infections, and "PSA anxiety":

"The potential benefit is finding a cancer that may harm the patient within his remaining lifetime. The disadvantage is what we call PSA anxiety, in other words concern on the part of the patient about having an undetected cancer in spite of a normal finding. The others are the risks of biopsy, which are sepsis, urinary tract infection without sepsis, bleeding, urinary retention... Interviewer: Are these common after biopsy or are they considered to be rare cases? J. B: They're unusual, I would say probably the nature of 4%, maybe 5%" —John D. Barry, Professor of Urology and of Surgery, Oregon Health and Science University, former chair of AUA

Other Elements of Bounded Rationality

Lack of Long-Term Thinking *"But I think what you cannot see as you make these initial decisions, because you're making them in the context of emotional turmoil, is what the long-term impact is. When you get a positive mammogram or a positive PSA, I don't think you're wondering about your sexual health 10 years from now, for example." —Patient Advocate*

Lack of Time: *"Of course the issue you cannot elaborate what your doctor mandates, but the question is, do many-- is there enough time for people to do that? I'm not sure about that". - To have the interaction with your physician, and talk about the harms and benefits. Of course, that would be quite ideally that there is also a physician involved, but I'm not sure whether there's enough time in the physician room to*

do that correctly." —Harry de Koning, Professor of Evaluation of Screening, CISNET comparative modeling group, PI of prostate cancer modeling group

Understanding Uncertainty: *"Actually, in..., I was very lucky. You don't get that kind of pressure. I did not have any trouble there. I think the difficulty is trying to get sort of readers, the public, interested in understanding these fine differences in risk. People don't want to talk about risks in that detail. Most people say, "Yeah, if there's cancer, let's get me away from it." So I think that's the challenge, is trying to get people to think about the degree of risk, and how to evaluate it for themselves. It's very difficult..."*—Media, Science Reporter

"Well, first of all a lot of is about belief. Basically it seems to be a good idea to early detect an invasive cancer and people all have to believe that since this seems such an obviously good idea it must be good. Then they tend to ignore the evidence entirely, or they have excuses why the evidence... [from a] randomized trial is not showing what they expect."—Peter Juni. MD-PhD, Director, Applied Health Research Centre, St. Michael's Hospital, and Professor of Medicine, University of Toronto

Risk aversion: *"I think that, yes, when you talk about the drawbacks and benefits of screenings, women are much more afraid of a cancer that is undiagnosed than having a screening and having the biopsy. You know, I'd rather have that knowledge and have that control than, you know, be thinking about cancers that I'm not doing. And once I do wind up with a cancer, and it's not-- and I could have caught it earlier. So, yeah, and it's the same thing, when they choose to have a mastectomy versus a lumpectomy, that many of them don't want the anxiety of having to go back for all these screenings and having to worry. They'd rather just know they did everything they could to get rid of every breast cancer cell they have in their body as much as they could."* —Deborah Kotz, Press Officer at FDA

"My mom was like, "It [insurance] covers it [mastectomy]," even though she had all these doubts, she was, "It's probably better that I just get rid of the possibilities of getting cancer in the future," and she kept on reminding herself that because I guess she needed some justifications as to why this is good for her, so I think she kept on reminding herself with that." —Patient Relative

Anecdotes: *"What many people respond to, however, are anecdotes. You hear about a women whose breast cancer was detected by mammography in her 30s or 40s, or PSA in a younger man that can seem pretty compelling. And anecdotes are really powerful, in fact we learn a lot from anecdotes and anecdotes are really important. But they're only one small piece of evidence and not usually the most useful piece of evidence. I think anecdotes drive some screening that's not necessarily warranted..."*— Matt Gillman, M.D., S.M. Director, Environmental Influences on Child Health Outcomes (ECHO); Office of the Director, National Institutes of Health

Specialty Perspective: *"I think at tumor board we sometimes see the outcome of too little too late. So yes, I think there are sad stories where someone just didn't go in for their mammogram for a couple of years and it comes back with this tumor. I think there are probably situations where people screen too much, but I think that it's hard to know what those are and I think that's what some of these public guidelines are trying to get at. I think, say patients are screened and they find a little lesion on a mammogram, and then a biopsy's done, and then the pathologist isn't sure whether it's absolutely benign, and then there's a surgery done. So you could argue for that patient, she had an extra biopsy, she had an extra surgery because*

of the screening. So I think those are two sides of the coin. I'll admit my bias that I'm a pathologist and I've seen the bad things that happen, that I'm pro screening if you want to know my bias." —Clinician

Fascination with New Technology: *"So I think there are a lot of professional reasons and just human, emotional reasons for the boom in screening. Plus, these companies are coming out with better and better and more sophisticated technologies, which always appeals to us Americans."* —Media, Science Reporter

Sources of Heterogeneity in Screening Guidelines and Practice

Interview data also suggested a huge variation across different countries and diseases, in terms of the use of scientific evidence base, risk perception of disease, treatment options, or trends (See APPENDIX H- Heterogeneity across Diseases, APPENDIX I- Heterogeneity across Countries)

Heterogeneity across Countries

"I believe in evidence. This is my major role and my major career, but I certainly believe in evidence. I think in many instances it is number one, certainly evidence-based, doing trials, doing quantification, and cost-effective itself, so it should be number one, but because you especially asked about how much screening is going on, and I think in the US, I think these public perceptions and industry are forcing it to do play a major role .." "...I think it should be peer quantification of the harms and the benefits, and from authoritative panels. I'm not sure if the US taskforce is that for the US. I think probably yes. There's politics involved, but I think nevertheless, I think we here in Europe should really believe in authoritative panels that are independent as possible and weigh the evidence that gets presented by the experts. I think that should be the situation. That should be the ideal situation." "... I think many doctors just have individual thoughts and ideas about that, and that plays a role, and that is why I think national programs like in the European countries where people are just invited independent of the physicians, it's very helpful in the sense that it gives you the correct information, and you can decide on your own. That's how in many European countries it's being done..."* —Harry de Koning, Professor of Evaluation of Screening, CISNET Comparative Modeling Group, PI of prostate cancer modeling group

Heterogeneity across Diseases

"We have very good therapeutic possibilities nowadays, I mean, that therapeutic window has become much larger than at the beginning of the '90...This was not the case in the '90s...this wide therapeutic window with breast cancer is important here. Again this contrasts with the narrow or the more narrow window that we have for colon cancer. You see, it is a very good idea to get colon cancer detected before it actually becomes a cancer, that's the polyps of course... But if not that then second best, to get it while it hasn't metastasized yet. So the situations are really, really different....In prostate cancer you see again the same reflected in a way. You see on one hand that indeed typically there aren't organized screening programs, systematic screening programs recommended [in Europe], because people are in agreement or tend to be in agreement, many of us of the public health community, that it may be problematic as well." —Peter Juni, MD-PhD, Director, Applied Health Research Centre, St. Michael's Hospital, and Professor of Medicine, University of Toronto

"It's a little bit easier to demonstrate the over treatment for PSA than it is for mammography, but it's interesting, and for years, I think, we were telling our patients, or at least I was telling my patients, oh, the PSA is a really limited test. We really need to be careful about how we use this. The benefits are very small

40

and the harms are significant...It's only been in the last few years that I think many of us have realized that mammography as a test itself is not that different from the PSA. It's a little bit harder to see the over diagnosis, which I think is one of the problems. With prostate cancer, we just know that there's so many low-grade prostate cancers that don't progress. There's probably, you know, there's also lots of breast cancers, but we just can't tell." —Nancy Keating, MD, PhD, Division of General Internal Medicine, Brigham and Women's Hospital, Department of Health Care Policy, Harvard

Discussion

There is widespread agreement that more may not always be better in health care, and that doing more can harm patients and generate excess human and monetary costs. In the context of screening, more may sometimes lead to unnecessary, invasive diagnostic procedures and treatment for tumors that would not have become clinically significant.

Reflecting this notion, the Institute of Medicine (IOM) National Roundtable on Health Care Quality coined the term "overuse" in 1998, adapting the definition of an inappropriate service mentioned the RAND Appropriateness Method User's Manual in the 1980's. Overuse was defined as "a health care service [that] is provided under circumstances in which its potential for harm exceeds the possible benefit." In 2008, the National Priorities Partnership identified eliminating overuse as a national priority, describing it as "unscientific," "redundant," and "excessive" care (Lipitz-Snyderman and Bach, 2013). More recently a whole theme issue of *BMJ* was dedicated to over-diagnosis (BMJ, 2015). However, the concept that sometimes doing less or even nothing may be better for patients still runs contrary to the mainstream medical philosophy of treating things when you find them; it is also non-intuitive (Ransohoff, 2002, 2010; Marshall, 2014). The term "evidence-based" suggests that guidelines simply emerge from scientific evidence, yet the historical fluctuations in PSA guidelines are not possible to attribute to changing underlying evidence. While the scientific evidence available to different actors may be the same, the weighting of the evidence can be very different, leading to differing interpretations and policy recommendations. It has previously been argued that guideline making is inherently a political process with its own decision-making structure, and differences in development methodologies and expert panel compositions are also likely to contribute to divergence between guidelines (Imperiale and Ransohoff, 2010; Pignone and Sox, 2008). Here I have presented the various elements of this decision-making structure, and have shown that the screening decision is subject to various sources of bounded rationality including feedback asymmetries, risk averseness, misperception of risk, short-termism, and delays in the process of policy formation.

I used an extended literature search, including published guidelines, to show that the reasons for these fluctuations should be sought in the internal structure where the screening decision is embedded, rather than in a changing external environment. This is similar to the persistent fluctuations observed in the Beer Distribution Game even when the underlying demand is kept completely constant (Sterman, 2000). Here I have shown that there was no event that legitimately caused the guidelines to expand followed by subsequent events that would cause them to narrow.

Such events would include technologies that changed the cost-benefit ratio significantly or some very large studies that really changed the perception of cost and benefits.

In addition to these sources of variation in formal guidelines and in their interpretation, the screening problem also has strong cognitive and psychological aspects. Perception of risk, risk literacy, and communication of scientific uncertainty are known to play a major role in affecting how people evaluate risk when making medical decisions (Operskalski and Barbey, 2016; Fischoff and Davis, 2014). Experts' disagreement about different guidelines is another dimension specific to the U.S., which adds to the existing problem. How laymen interpret expert disputes is a subject which has not been explored extensively in the context of screening, but recent research shows that laypeople tend to use narrow attributions to make sense of these disputes (Dieckman et al., 2015).

The asymmetrical impact of experience on perceived risks has also been shown to be potentially important: A negative result from the screening is a non-event, but a positive one is a huge event that changes perceived harm and benefits significantly. As more and more men are given a cancer diagnosis by screening, the natural perception of each "survivor" is that screening "saved" his life, although a large fraction of survivors actually have a type of prostate cancer that could have been treated as effectively if found later, or that would not have caused any problems during their lifetimes. The problem is that for each "survivor," there is no way to know whether screening and the treatment "caused" survival, in the absence of the counterfactual. Thus the number of men who perceive benefit from screening is substantially greater than the actual number who receive benefit, and the impression of benefit gets exaggerated due to this imbalanced, missing feedback.

It is important to note that while the available evidence base may be different for different types of cancers, the reinforcement operates similarly for other screening decisions. This case study of the history of PSA screening in the U.S. provides good insight into the strength of the forces in play. Even if some screening tests work better than the PSA test, or even if the PSA test itself eventually is demonstrated to provide some benefit, these reinforcing forces will always be operative, independent of the benefit-and-harms environment. Sometimes they may work in the same direction and at other times they may work in the opposite direction of what the evidence is suggesting. This implies that the screening decision is overwhelmed by other individual factors and biases and is largely independent of the scientific evidence base. Many medical screening decisions and guideline formation processes are inherently subject to these biases.

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Essay 2: Our Walk to the End of Cancer? Understanding Long-Term Trends in Medical Screening

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Abstract

In this study we develop the first integrated, broad boundary feedback theory and formal model to explain the dynamics of medical screening. The theory includes a decision-theoretic core around harms and benefits including the fundamental tradeoff between sensitivity and specificity; and feedbacks that condition guidelines and actual practice. To provide context we use the case of PSA screening for prostate cancer as a motivating example, but our model is generic and applicable to other contexts such as mammography. We present a behaviorally realistic, boundedly-rational model of detection and selection for health screening that creates oscillations in policy recommendation thresholds of formal guidelines. This core model, entailing only the evidence generation and translation processes, demonstrates how oscillations are natural to this category of problems due to inherent delays in evidence-based screening. These fluctuations lead to long periods during which screening guidelines are suboptimal.

Keywords:

Introduction and Motivation

The classical approach to setting evidence-based screening guidelines is based on the statistical paradigm of Type-I and Type-II errors, seeking to find an evidence-based balance between sensitivity (and thus the risk of false positives) and specificity (and the risk of false negatives), given the costs and benefits of different outcomes. This is the first step in decision making, involving only the available scientific evidence, which is, in principle, the same for all decision makers.

Despite this universal nature of the evidence base, to date we still have only a limited understanding of screening dynamics and its consequences. Clinical Practice Guidelines (CPG's) for routine screening such as PSA testing or mammography vary substantially in the United States when compared to Europe, and often are not followed by clinicians and patients, with significant over-screening for some tests and under-screening for others. Guideline making is argued to be an inherently political process with its own decision-making structure, and differences in development methodologies and expert panel compositions are also likely to contribute to the observed divergence between practice guidelines (Imperiale and Ransohoff, 2010; Pignone and Sox, 2008).

Figure 1 shows the variation and fluctuations in policy decision thresholds of prostate cancer for the most commonly used prostate cancer screening guidelines developed in the United States: 1- U.S. Preventive Services Task Force (USPSTF), 2-American Cancer Society (ACS), 3-American Urological Association (AUA), and 4- National Comprehensive Cancer Network (NCCN).
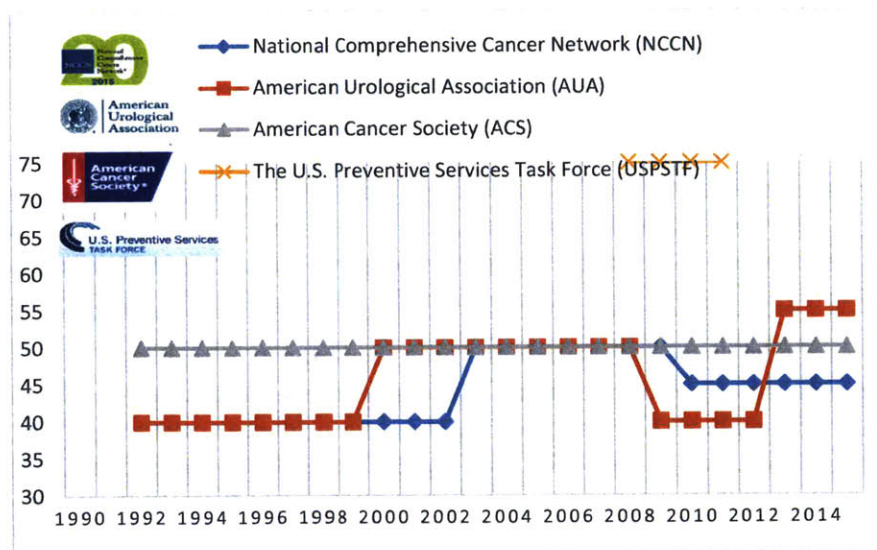
Figure 1 Data collected for recommended PSA starting age for asymptomatic men

Recommended changes in several common disease definitions mainly resulted in the expansion of the eligibility criteria for disease, with an apparent increase in disease incidence and prevalence (Hoffman and Cooper, 2012; Croswell et al., 2010; Esserman et al., 2014). There is growing evidence of over-screening and resulting overtreatment in certain areas (Ahn et al., 2014; Black, 2000; Bleyer and Welch, 2012; Etzioni et al., 2002), and significant variation in published practice guidelines, with fluctuations in breadth indications for screening. Most practice guidelines still differ with respect to

50

their selection criteria, including the recommended starting age for routinely discussing screening, or the criteria for biopsy referral. Based on 2010-2012 data, 39.6% of Americans will be diagnosed with some kind of cancer at some point during their lifetime (National Cancer Institute, 2016), which is of particular concern with a growing aging population.

There is widespread agreement that more may not always be better in health care; it may generate more harms than benefits. In the context of screening, more may sometimes lead to unnecessary, invasive diagnostic procedures and treatment for tumors that may not be or ever become clinically significant. Reflecting this notion, the Institute of Medicine (IOM) National Roundtable on Health Care Quality coined the term "overuse" in 1998, adapting the definition of an inappropriate service developed in the 1980's. Overuse was defined as "a health care service [that] is provided under circumstances in which its potential for harm exceeds the possible benefit." In 2008, the National Priorities Partnershiphttp://archinte.jamanetwork.com/article.aspx?articleid=1691771 identified eliminating overuse as a national priority, describing it as "unscientific," "redundant," and "excessive" care (Lipitz-Snyderman and Bach, 2013). More recently, the British Medical Journal dedicated an entire issue to over-diagnosis (BMJ, 2015). However the concept that sometimes doing less or even nothing may be better for patients still runs contrary to the mainstream medical philosophy of treating things when you find them; it is also non-intuitive and contrary to heuristic thinking (Ransohoff, 2002, 2010; Marshall, 2014) identified eliminating overuse as a national priority, describing it as "unscientific," "redundant," and "excessive" care (Lipitz-Snyderman and Bach, 2013). More recently, the British Medical Journal dedicated an entire issue to over-diagnosis (BMJ, 2015). However the concept that sometimes doing less or even nothing may be better for patients still runs contrary to the mainstream medical philosophy of treating things when you find them; it is also non-intuitive and contrary to heuristic thinking (Ransohoff, 2002, 2010; Marshall, 2014)

The motivation of this study is to develop a feedback-rich theory to explain the dynamic nature of the medical screening problem within the U.S. context that is firmly grounded in empirical evidence. After having established the underlying structure responsible for overshoot and undershoot of indications for screening (a normal but undesired adaptive condition of the internal environment), ways of monitoring, diagnosing, and managing of these conditions can be investigated.

I seek to create a model that is both generic enough to be adapted to other cases of medical screening, and realistic enough to replicate basic dynamics concerning cancer screening, including noncompliance with medical recommendations. Since the incidence of screening differs substantially across countries and diseases, we will also explore other dimensions of this variation across countries, and across different screening tests for other diseases. By providing both qualitative and quantitative evidence I aim to document variations in guidelines and actual practice across several dimensions.

Figure 2 shows the American Urological Association's published guideline methodology for the proper influence of evidence and interpretation on policy creation. The framework follows the Institute of Medicine's recommendations for guideline development, including a systematic review of the evidence by a multidisciplinary panel (Carter et al., 2013). Evidence reviews lead to evidence interpretation and then policy, with no feedback incorporated/considered at any of these steps. This

example is representative of the linear thinking prevalent in policy formation and interpretation, and illustrates that broad boundary feedbacks are largely ignored in existing frameworks and mindsets.

Dynamically complex policy problems have numerous characteristics that inhibit both the making and the implementation of effective policies, which necessitates endogenous perspectives. A broad boundary framework is needed to support evidence-based guideline development (the policy formation) and to explain how screening criteria evolve over time.
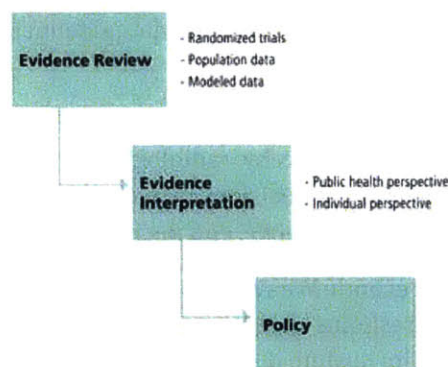
Figure 11 Influence of evidence and interpretation on policy creation, AUA guideline methodology. Source: https://www.auanet.org/education/guidelines/prostate-cancer-detection.cfm

Background

This study builds on a large literature on human judgment and decision making applied to policy decision thresholds. Hammond and Swets were the first to propose a hypothesis about the dynamics of policy thresholds. Swets played a key role in adapting signal detection theory to the psychology of perception (Swets 1964, Green and Swets, 1966) and later as a central tool called the "receiver operating characteristic" (ROC) curve used in medical diagnostics (1966). He was the first to describe shifted and cycling thresholds. Pauker and Kassirer (1980) described the threshold approach to clinical decision-making and suggested a concept called "the therapeutic threshold"—a probability of disease that constitutes a point of indifference. Later, Schlesinger (1986) proposed the concept of "regular oscillations" in the dominance of political parties, in his book "The Cycles of American History".

In his famous book on human judgment and decision making, Hammond (1996) proposed that policy thresholds may oscillate over time due to opposing pressures coming from constituencies representing those treated unfairly. According to Hammond (1996), any uncertain test which employs a threshold used as a decision tool would lead to some error and yield unavoidable injustice to some constituency; namely, the false positives and the false negatives. This would lead to opposing pressures lobbying the policymakers to move the threshold, causing cycling of that decision threshold over time. He argued that there are oscillations in public and professional attitudes with implicit policy thresholds, and that those cycles would last about 30 years across decision domains (Hammond, 1996). According to him: "*If such oscillations can be shown to exist, and if they can be shown to have a definite period . . . then we have at hand not only a means for predicting our future*

political climate far in advance, but an important phenomenon that strongly invites, indeed, demands, analysis and interpretation."

There is a related line of research that suggests that not only the policy decision thresholds, but also the physicians' decision thresholds may vary over time. Research shows a wide variation among radiologists' decisions "regarding the interpretation of mammograms and the appropriate tradeoff between false positives and false negatives" (Stewart and Mumpower, 2004; Swets et al., 2000). This conflicts with the long-held assumption that the clinicians' accuracy of judgments is fixed, and suggests that not only the thresholds suggested by formal guidelines, but also the physicians' decision thresholds may fluctuate.

Stewart and Mumpower (2004) describe three domains of decision making about mammography screening, focusing on the decisions made by radiologists in their practice, and the variation in radiologists' decisions. These include the decisions by women and their doctors to obtain screening, decisions by radiologists to recommend biopsy, and decisions of policymakers.

In the system dynamics domain, recently Weaver and Richardson (2006) published a theory-building article on the cycling of policy thresholds postulated by Hammond and other scholars (Swets, 1992; Schlesinger, 1986). Based on a prior system dynamics model, they first present a simplified theory of Hammond's initial insight and then present three alternative models: one with delays in policy-maker responsiveness; one with stakeholders' shifting constituencies in response to recent errors; and one with integral control representing the historical dissatisfaction of competing constituencies (Weaver and Richardson, 2006).

The literature of research on human judgment and decision making also ties closely into the broader theoretical research on threshold learning, reinforcement, learning to make selection and detection decisions, and how psychological research improves diagnostic decisions (Swets, 2000; Swets, 2001; Stewart and Mumpower, 2004; Stewart et al., 2011; Erev et al., 1995; Erev, 1998).

Methods

The motivation of this study is to develop a dynamic hypothesis to investigate the underlying structure that accounts for oscillations in screening indications and the over-screening trend for cancer in the U.S., which leads to over-diagnosis and over-use of health services. This requires revealing the causal structure of a dynamic problem that involves the feedback relationships between system variables with respect to the past behavior of the system.

My dynamic theory is grounded in empirical evidence and we use a mix of qualitative and quantitative methods and a dynamic modeling approach to complex systems to explain the medical screening problem within the U.S. context (Forrester, 1961; Sterman, 2000). I employ semi-structured expert opinion interviews, a medical literature search, and empirical data collection on how PSA screening criteria have evolved over time.

Interviews are conducted with a purposive sample of 34 health and medical professionals, including clinicians, policy makers from the American Cancer Society, American Urological Association, and the U.S. Preventive Services Task Force; academics and Cancer Intervention and Surveillance Modeling

Network (CISNET) group members; advocacy and activist group members; patients and relatives; and media reporters/science writers who publish on screening-related issues in various outlets. A semi-structured interview outline was developed to investigate different sources of variation in screening guidelines and actual practice, and to gather different expert opinion perspectives regarding the screening decision (see Appendix C-E). I used the snowball method, in which I asked each interviewee who else we should talk to, and continued until getting to the point of diminishing returns on new ideas, and covering all the major groups of participants.

Ultimately I formulated a system dynamics (SD) model that consists of a set of coupled differential equations. The problems around cancer screening are particularly suited to SD modeling because of the presence of many time-related phenomena, nonlinearities, and delayed feedbacks.

Medical Screening Model Overview

I will now present a generic/stylized model to explore and formalize the available evidence in population screening. I start with a small policy structure, then embellish it gradually, by adding one layer at a time, while testing the model structure and its outputs throughout this process.

The "Core Model" provides the foundation for the development of evidence-based screening guidelines. The "Model of Actual Practice" extends and integrates the "Core Model" with the "Interpretation and Implementation of Formal Guidelines."

The generic model and the extended model for the PSA case study will be firmly grounded in empirical evidence. A mix of qualitative and quantitative methods will be used to explain the dynamic nature of the population-level health screening problem. While the screening debate is almost a universal problem and not specific to the United States, I will mainly treat the problem within the U.S. context, while providing a wider perspective on the issue using comparative evidence from other developed countries and other diseases.

Figure 3 shows the boundary of the model, indicating the endogenous variables, exogenous variables for which parameters or time series are used as an input for the simulation time horizon, and other variables that are intentionally left outside of the system. The model boundary is broad enough to capture the causal mechanisms that drive the system behavior (Forrester, 1987). Since PSA screening started in the late 1980's and historical data is available till about 2015, the time horizon of the model is 1980-2040, in order to capture the long-term effects of policy options.

Figure 4 gives the full model overview, showing the key feedback structure (B's represent balancing, and R's represent reinforcing feedback loops, numbered). The two most important state variables are the Threshold Value (T), and the Recommended Starting Age (R). Time-constant parameters are

indicated in blue. Separate causal loop and stock-flow diagrams can be referred to for a more detailed view.
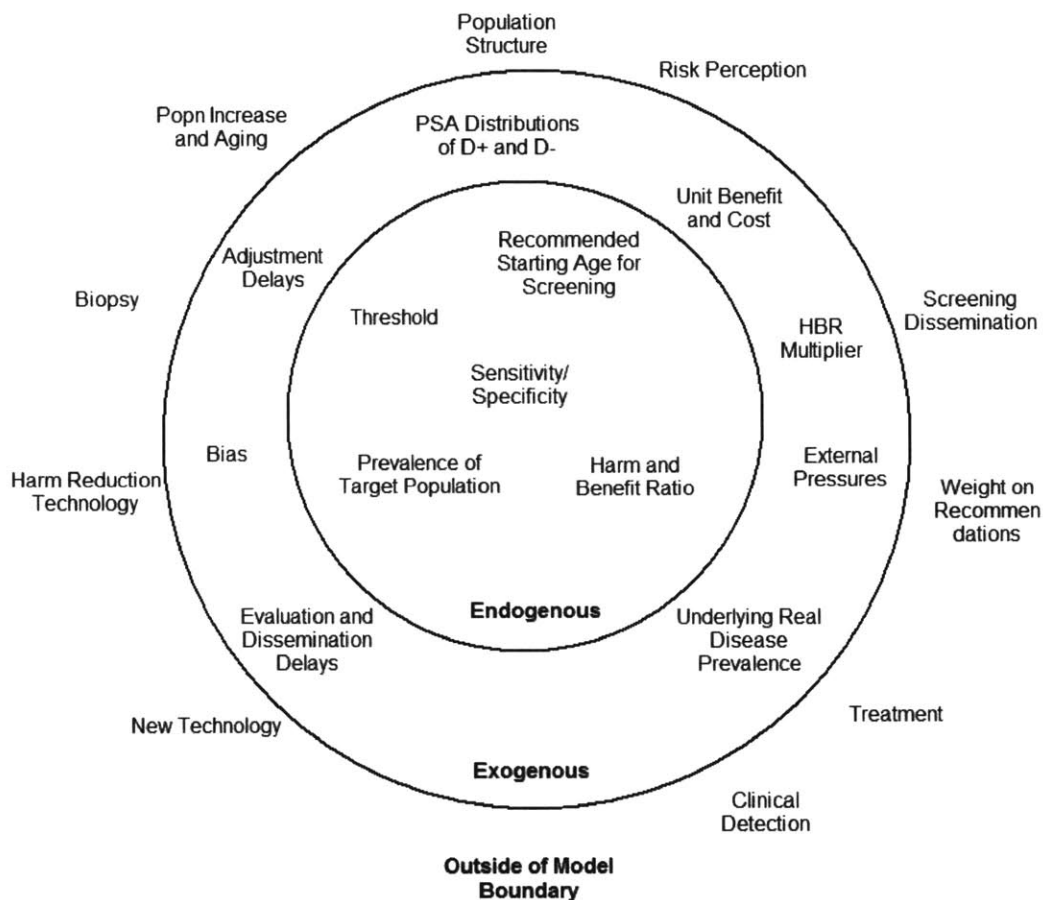
Figure 12 Model Boundary Diagram of the Core Model (Classical Approach to Setting Formal Guidelines)

Model of Classical Approach to Setting Formal Guidelines

At the core of all evidence-based guidelines there is a decision-theoretic framework which is the first and fundamental step in medical decision-making. Ideally, this first step only involves the available facts and analysis of evidence. For routine screening, available facts include a description of the available options (screening or not screening), the possible outcomes of those options (cases of cancer diagnosed, lives extended, the effort of screening and workups, the effect of false-positive results, and harms), and the probabilities that any of these outcomes may occur.
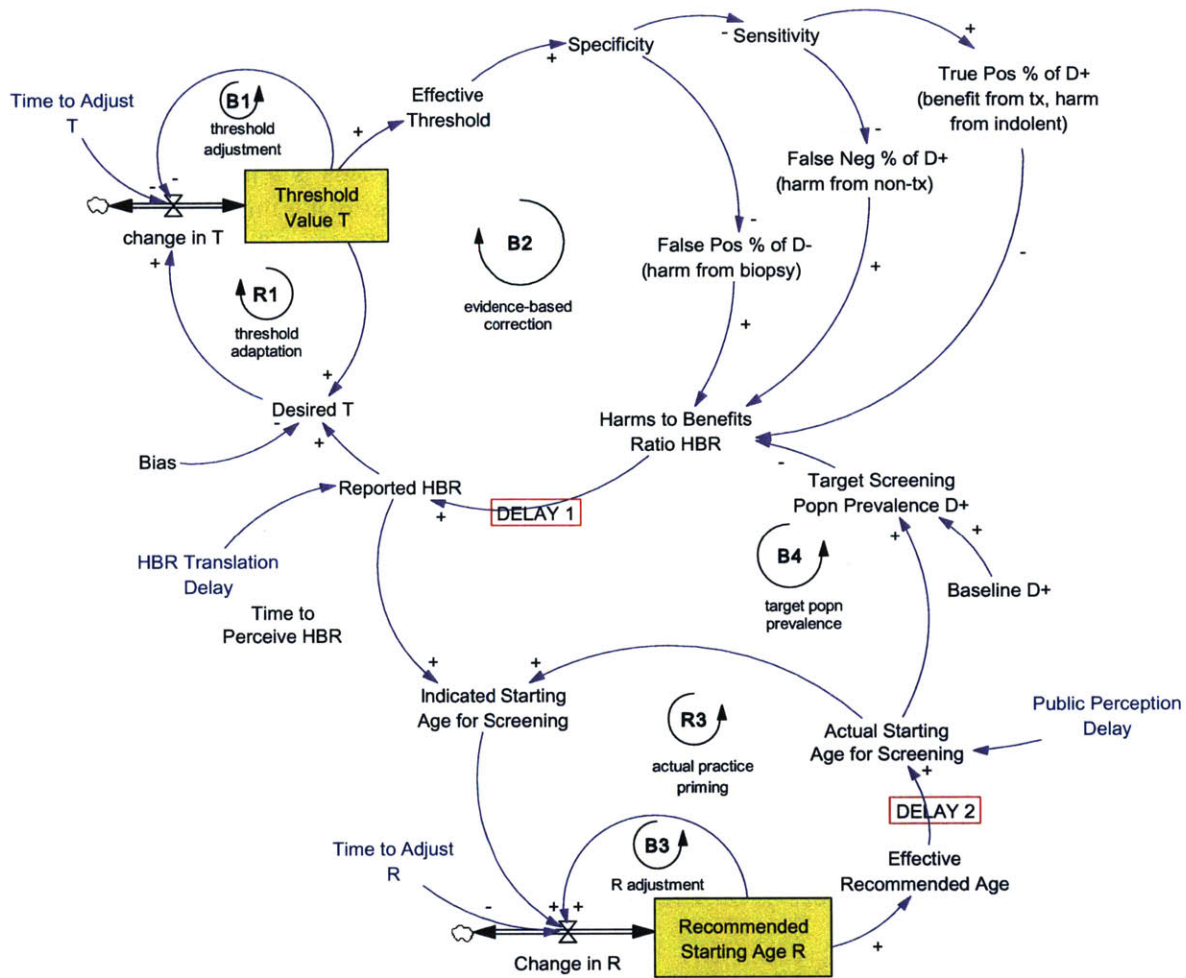
Figure 13 Simplified Overview of Full Model Showing the Key Feedback Structure

Policy Structure for Development of Evidence−Based Screening

The Evidence-Based model causal structure shows how potential harms and benefits lead to balanced decision making, and how the threshold of a screening test is ideally determined based on available evidence. The B1 balancing feedback loop closes any gaps between the desired and the actual threshold value T. The goal itself depends on the state of the system, the threshold value T, creating the R1 loop, threshold adaptation. As long as the net effect of the pressures on the threshold goal causes T* to exceed T, the threshold will grow exponentially; otherwise it will decay exponentially.

The B2 loop in the center reflects the influence of harm and benefit evaluations of screening, and how a natural balance can be established by looking at the Harm-to-Benefit Ratio (HBR). Note the information delay between the actual and perceived HBR, which indicates the time delay required

56

for the HBR evaluation process by the scientific and medical community. This evaluation delay can be on the order of years and has possible implications for screening outcomes.

The main stock variable of this structure is the Threshold Value T, which represents the cutoff value for the test outcome. Values above T are considered to indicate a positive (unhealthy) result; values below T indicate a negative (healthy) result. We used a simple Hill-Climbing structure to indicate the optimal operating point around T (Miller, 1998; Sterman, 2000). This is a plausible heuristic to explore the trajectory of the biopsy threshold where the optimal value of it is unknown. To model hill climbing in our context, the Desired Threshold (T*) is anchored on the current state T, and then it is adjusted by the reported HBR and other possible external pressures representing the gradient of the "hill" and indicating the way uphill (Sterman, 2000). Other possible pressures include pressures from patient advocacy groups, payers, the public, etc. The effects of the HBR and the external pressures on T* (α_{hbr} and α_p) are formulated as multiplicative. The structure for the hill-climbing process is as follows:

$$T_i = \int (\frac{d}{dt} T_i, T_{i0})$$ (1)

$$\frac{d}{dt} T_i = \frac{(T_i * - T_i)}{\tau_i}$$ (2)

$$T_i^* = T_i \times \alpha_{hbr} * \times \alpha_p , \text{ where}$$ (3)

T* is the Desired threshold implied by the HBR and other external pressures, and τ is the Threshold Adjustment Time. Function for desired Threshold T^* is given as an increasing function of HBR and other external pressures. Let us define the lag operator £ (): £ (x, t) to be the 3rd order exponentially smoothed value of x, with time constant t.

$$\alpha_{hbr}^{t*} = £ (HBR, \gamma)^{\beta_i}$$ (4)

$$\alpha_p = \delta^{\varepsilon_i}$$ (5)

$$\frac{d}{dt} T_i == \frac{((T_i \times £ (HBR_{i,}, \gamma_i))^{\beta_i} \times \delta^{\varepsilon_i}) - T_i)}{\tau_i}$$ (6)

The harm-to-benefit ratio is an overall aggregate performance measure that indicates the ratio of possible harm to benefit of routine screening. Possible harms of screening include failing to treat false negatives and treating false positives. Possible benefits include treating true positives to prevent cancer death, or to increase the quality of life of the patient. Harms associated with screening include anxiety, distress, and other psychological responses, false positive and false negative test results, unnecessary follow-up testing and over-diagnosis (finding cases that would not have clinically

surfaced in the patient's lifetime). Professor Matt Gillman lists potential harms and benefits as follows[2]:

"[Benefits are] saving lives, improving quality of life. Interviewer: Harms of screening? MG: Potential harms? Well you have the harms of screening itself, so the screening test may be expensive or painful or difficult, and then you have the follow up of the false positives which may be expensive, difficult, painful, and anxiety producing. So that's all about the test. Now once you have a positive test, a positive screen, you still may have harms because of the treatment. In a screening paradigm, if there's 100% adherence everyone who gets a positive screen, maybe then gets a diagnostic test and then treated, that process can have harms. /..So there are harms of the screening process and then there are harms that accrue the people who are positives. Now if they are false positives they can only get harm, they can't get benefit. If they are true positives they can get benefit but they can also get harm." — Matt Gillman, M.D., S.M. Director, Environmental Influences on Child Health Outcomes (ECHO); Office of the Director, National Institutes of Health

The Harm-to-Benefit Ratio is defined as: $HBR_i = \dfrac{\Delta H_i}{\Delta B_i}$ where (7)

Total net benefits and net harms are calculated by summing over four possible outcomes, true positive rate (TPR), false positive rate (FPR), true negative rate (TNR), and false negative rate (FNR). Unit benefits and harms are the utility and disutility values associated with a screening test. Accordingly, all true positive and negatives are assigned a non-negative net benefit; and all false positive and negatives are assigned a non-negative net harm in the model.

Policy Structure for Guidelines in Use — Breadth of Selection Criteria

The structure below is formulated to represent the role and influence of interpretation and implementation of CPG's, and more specifically, how the "selection criteria," or the "breadth of indications," have evolved over time, such as the starting age or the threshold for biopsy. For our case analysis, we picked the decision for the Recommended Starting Age for Routine Screening as a proxy for breadth selection criteria.

Figure 5 shows the policy structure for guidelines in use, and the role and influence of the advocacy groups on breadth indications. The main state variable is the Recommended Starting Age for Routine Screening. This structure generates the breadth of selection criteria for the screening population, or the fraction of the population considered to be candidates for screening. The target population is determined by the Recommended Starting Age for Routine Screening, and the Actual Starting Age gives us the actual practice. Perception and implementation delays between the recommendation and the actual starting age for screening, and the recommendations themselves, vary between institutions within the U.S.

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[2] Prof. Gillman provided input while he was professor of population medicine at Harvard Medical School and a member of the USPSTF. He is now director of the NIH program Environmental Influences on Child Health Outcomes. The views he expresses are his own.

$$R_i = \int (\frac{d}{dt} R_i, R_{io})$$

(8)

$$\frac{d}{dt} R_i = \frac{(R_i * - R_i)}{\lambda_i}$$

(9)

There are two factors that motivate the change in breadth of selection criteria. First, as radiologists and practitioners adapt to new technologies that enable earlier detection of cancer, policymakers will tend to expand the criteria to include those patients for whom the inclusion appears to make an effective screening possible. Second, if benefit-and-harm evaluations reveal that the screening test's perceived benefits are lower than desired, this will cause policy makers, and consequently medical practitioners, to gradually become more selective in their screening target population; that is, they will narrow the selection criteria in order to improve future evaluations.

The R1 loop represents this inclusion drive for the screened population, while the B1 loop represents the change of direction for the selection criteria based on evaluation of screening harm and benefit in a longer term. Note that the structure has two implicit delays embedded in these policy decisions: 1) the modification delay for the effective recommended starting age (λ), and 2) the evaluation or translation delay for the benefits and harms of screening (Υ). Because this evaluation process takes time to complete, evaluations may fail to reflect the impact of the latest changes in screening guidelines. This "moving target" situation for screening guidelines can be even more problematic if λ is short and Υ is long. Let us now discuss the specifics of the model formulations.

$$\theta R_i = \pounds(R_i, \phi_i)$$

(10)

$$\rho HBR_i = \pounds(HBR_i, \gamma_i)$$

(11)

$$\alpha_{hbr}^{r*} = 1 + \alpha_{hbr} \times ((\pounds(HBR, \gamma) - 1)$$

(12)

$$R_i* = \pounds(R_i, \phi_i) \times (1 + \alpha_{hbr} \times (\pounds(HBR, \gamma) - 1))$$

(13)

The Actual Starting Age for Routine Screening (ϕR_i) is formulated using a simple adaptive expectation structure, which is a realistic way to model the way people update their beliefs and perceptions. Patients are found to be mostly affected by their individual health care providers while making the decision to have a screening test, and hence generating an update regarding recommendations involves several stages of information processing. These include the response time of individual hospitals, doctors, and radiologists to adopt the guidelines and diffuse it into the system, and the average time required by the public to perceive, process, and comply with the recommendations. Hence the Public Perception Delay (Φ) is modeled as a third-order smoothed average of R, where Φ reflects the total reaction time to process and respond to changing recommendations.

The Age-specific Prevalence D^+ represents the fraction of histological, screen-detectable cancer in the target screening population. Empirical studies based on autopsy data show that the histological prevalence of cancer is an increasing function of the individual's age (Harach et al., 1985, Nielsen et al., 1987; Montle et al., 1989) and there are racial differences in prevalence between Caucasian-American, African-American, and Caucasian-Mediterranean men (Haas et al., 2008; Jahn et al., 2015; Bell et al., 2015.) We assumed that the underlying real disease burden is stable during the simulation

time horizon, and only increases by age with a certain slope (Ω). Initial prevalence at the Baseline Age (Ψ) is assumed to be zero:

$$D^+ = MIN(1, MAX(0,((\text{£}\,(R,\phi)-\Psi)*\Omega) \tag{14}$$
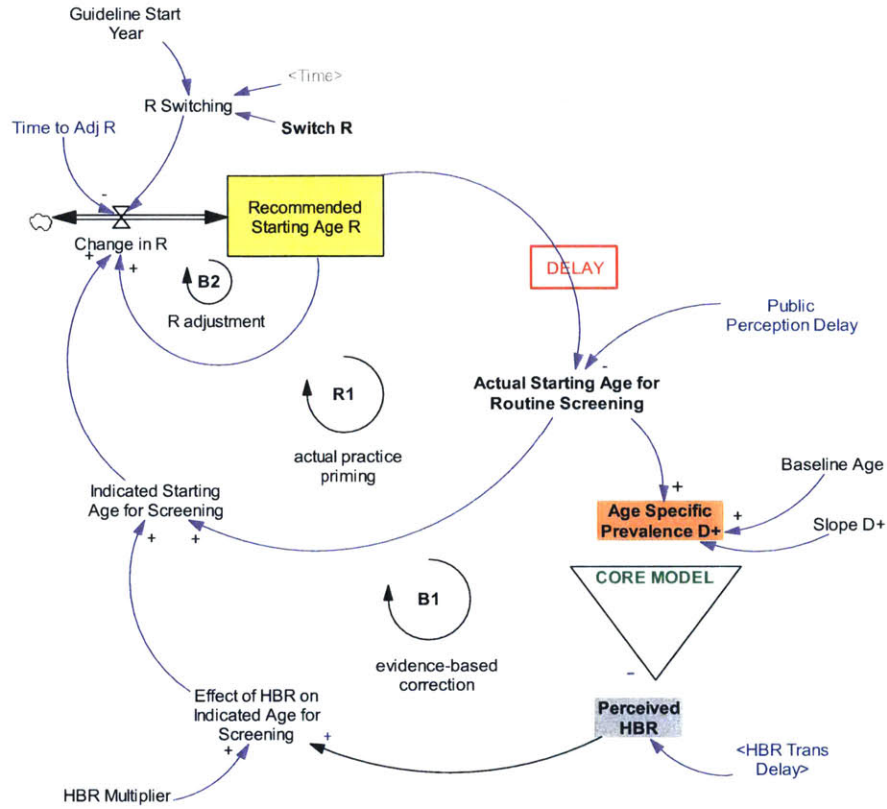
Figure 14 Model of Actual Practice: Policy Structure for Guidelines in Use

For any given population prevalence for a specific target population, our decision-theoretic model calculates the HBR and the Perceived/Reported HBR. Increasing levels of the perceived HBR increase the Effect of HBR on Indicated Age for Screening, EffofHBRonR$_i$*. As perceived HBR increases above its reference value of 1, the effect of HBR becomes higher than 1, and hence shifts the Indicated Starting Age R$_i$* above the Actual Starting Age for Routine Screening. If the perceived HBR reaches its optimal level of 1.0, the R$_i$* becomes equal to the Actual Starting Age, ActualR$_i$. The Recommended Starting Age for Routine Screening is formulated as the output of an information delay structure, where the delay parameter is represented by the Time to Adjust R, or λ_i. This parameter gives the delay time constant for the adjustment time of R.

$$\frac{d}{dt}R_i = \frac{((\theta R_i \times(1+\alpha \times \rho HBR_i))-R_i)}{\lambda_i} \tag{15}$$

$$= \frac{((\text{£}\,(R_i,\phi_i)\times(1+\alpha \times \text{£}\,(HBR_i,\gamma_i))-R_i)}{\lambda_i} \tag{16}$$

PSA Model Specifications

Table 1 lists all model inputs and symbols used throughout the paper with base case values.

Table 4 List of Model Inputs

Threshold T	Symbol [unit]	Base Case	Description
Threshold Value	T [dmnl]	[4]	Threshold, or cutoff value, for the test outcome. Values above T are considered as test positive
Time to Adjust T	τ [year]	[1.5]	Adjustment time constant for the rate of change of the Threshold T
Location Parameter of Lognormal Distribution∈R	μ^+ μ^- [dmnl]	1, 0.3	Location parameter of the associated normal distribution of the test outcome for D⁺ and D⁻
Scale Parameter of Lognormal Distribution>0	σ^+ σ^- [dmnl]	0.6, 0.3	Scale parameter of the associated normal distribution of the test outcome for D⁺ and D⁻
% Prevalence	% D⁺	0.3	Proportion of D⁺ in target screening population
Baseline Age	Ψ [dmnl]	30	Baseline Age
Slope D⁺	Ω [dmnl]	0.012	Rate of change in prevalence per age year
Influence of External Pressures	δ	[1]	Potential influence of external pressures, such as advocacy groups
Unit Benefit$_{j,k}$ (j=T⁺,T⁻; k=D⁺,D⁻)	$UB_{j,k}$ [dmnl]	$UB_{j,k} = \begin{bmatrix} 3 & 0 \\ 0 & 0.5 \end{bmatrix}$	Non-negative unit benefits for possible test outcome and disease state pairs
Unit Harm$_{j,k}$ (j=T⁺,T⁻; k=D⁺,D⁻)	$UC_{j,k}$ [dmnl]	$UC_{j,k} = \begin{bmatrix} 0 & 0.5 \\ 1.5 & 0 \end{bmatrix}$	Non-negative unit harms for possible test outcome and disease state pairs
HBR Translation Delay	γ [year]	[10]	Time constant for translation of HBR (Harm-to-Benefit ratio)
Strength Eff of Ext Pres	ε [dmnl]	0	Sensitivity of External Pressure's effect on Threshold T
Strength Eff of HBR	β [dmnl]	0.3	Sensitivity of HBR ratio's effect on Threshold T.
Recommended Starting Age	R [ages]	[50]	Initial Recommended Starting Age for routine screening

			Adjustment time constant
Time to Adjust R	λ [year]	[1.5]	for the rate of change of the Recommended Starting Age, R
Public Perception Delay	ϕ [year]	2	Average time required to perceive the recommendation
HBR Multiplier	α [dmnl]	[0.3]	Multiplier for the effect of HBR on starting age of screening

Diagnostic Parameters

The classical approach to setting guidelines for screening is to seek an evidence-based balance between the sensitivity and specificity of a diagnostic test. "Sensitivity" means the medical test's' ability to correctly identify positive cases, measured as the proportion of people who are known to have the disease and who also correctly test positive for it. "Specificity" means the test's ability to correctly identify the negative cases, defined as the proportion of individuals who are known to be healthy and who will also correctly test negative for the disease.

If we consider the results of a particular test in two hypothetical populations, one population with a disease and the other population without the disease, we rarely observe a perfect separation between these two. Indeed, the distributions of their test results more or less overlap. Assuming that D^+ and D^- indicate persons coming from these diseased and healthy populations, and T^+ and T^- indicate positive and negative test results with respect to a certain test result value, there are four possible outcomes for a medical screening test (Figure 6). Hence there will always be a Type I (α) and a Type II (β) error when we try to separate these two populations, the error being higher as the overlap between populations with respect to the assay value gets higher.

We assume that the total PSA values of diseased (D^+) and healthy (D^-) populations can be reasonably approximated by a log-normal distribution. With selected base case parameters for the location and scale parameters μ and σ the mean total PSA values of D^+ and D^- populations become 3.25 and 1.46 ng/ml. Figures 7a and 7b give the probability and cumulative distribution functions of the test outcome for D^+ and D^- with base case parameters. Figures 7c and 7d show a histogram of total PSA values for U.S. men from NHANES 2001-2002, and empirical values versus simulation for the CDF of the test outcome.

Disease State
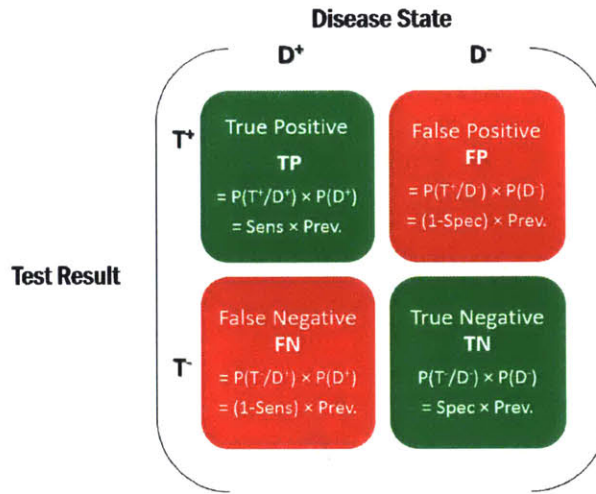
Figure 15 The Decision Matrix: Potential results of a screening test (T⁺ test positive, D⁺ disease present)
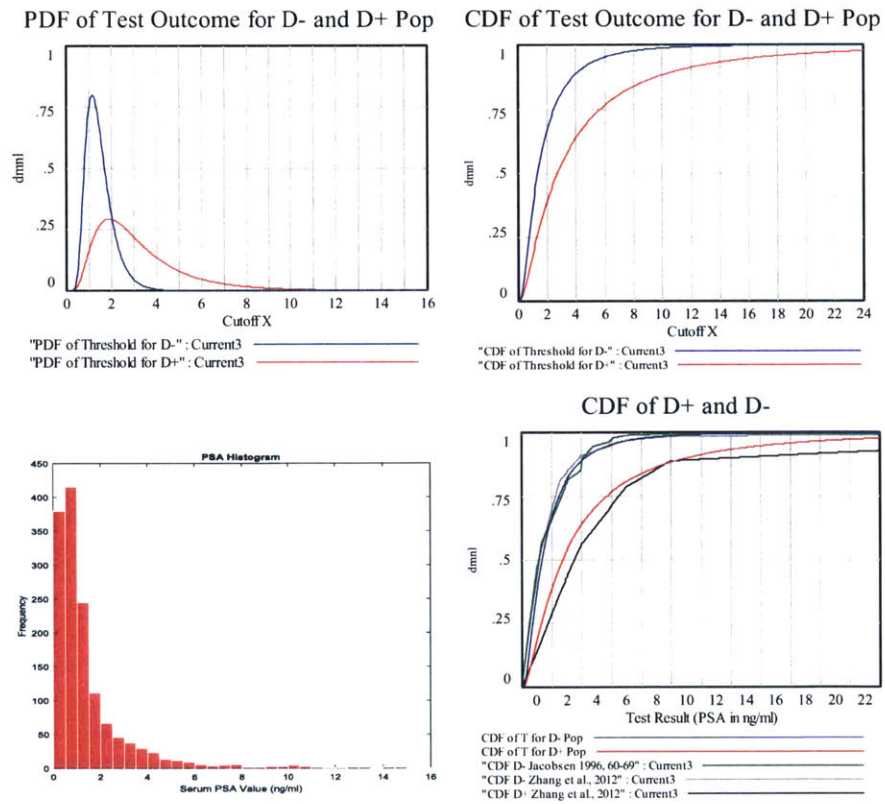
Figure 16 a) Probability and b) cumulative distribution functions of the test outcome for healthy (blue, D⁻) and diseased (red, D⁺) with base case parameters, c) Histogram of PSA observations from NHANES 2001-2002, d) Empirical CDF's versus simulation

63

Diagnostic Performance: Receiver Operating Characteristic (ROC) Curve

The ROC curve is the most commonly used tool to evaluate the diagnostic performance of a screening test (Metz, 1978; Zweig and Campbell, 1993), and can also be used to compare the diagnostic performance of two or more different tests (Griner et al., 1981). In a ROC curve, the True Positive Rate (TPR) is plotted against the False Positive Rate (FPR) for different cutoff or threshold points of a criterion value. Hence every point on the curve represents a sensitivity and specificity pair corresponding to a particular decision threshold (see Figure 8a). The 45-degree line represents the case where there is no ability to distinguish between the diseased and healthy populations, or when the test has no value-added. The ROC curve shows the overall performance of the test and it does not answer the question of the choice of the Threshold value T.

The "ideal" test with perfect discrimination (where there is no overlap in the two distributions) would have a ROC curve that passes through the upper left corner (100% sensitivity/100% specificity point). Therefore, the closer the ROC curve is to the upper left corner, the higher the overall accuracy of the test will be (Zweig and Campbell, 1993). It would be desirable to have 100% sensitivity and 100% specificity, as this would perfectly discriminate those with the disease from those without, with no false positives or false negatives. However, sensitivity and specificity are not independent, which suggests the fundamental tradeoff of finding a balance between the two.
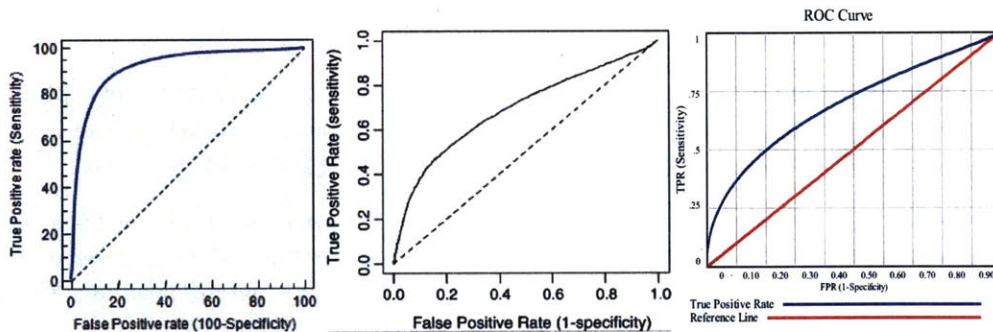
Figure 17 a) A typical, theoretical ROC curve (Source: medcalc.org) b) Empirical ROC for PSA (Source: Zhang et al., 2012) and c) Simulated ROC Curve

Figure 8a shows empirical ROC curves for PSA testing from Steuber et al., 2008, Underwood et al., 2012, Jacobsen et al., 1996, Etzioni et al., 2004, Ferro et al., 2015., Thompson et al., 2005, Zhang et al., 2012, and Ahn et al., 2014. Figure 8b gives the 45-degree indifference line (black line) and the model ROC curve (red line).

The area under the ROC curve (AUC) is another metric that indicates how well a screening test can distinguish between the two diagnostic groups. Higher values of AUC indicate a higher discriminatory power. The empirical fitted AUC estimates with respect to discrete occurrence of prostate cancer range from 0.57 to 0.77: estimates include 0.577 (Ahn et al., 2014), 0.639 (Ferro et al., 2015), 0.678 (Thompson et al., 2005), 0.72 (Jacobsen et al., 1996), 0.74 (Etzioni et al., 2004), and 0.77 (Zhang et al., 2012). The simulated ROC curve gives an AUC of 0.72 with base case parameters.

ROC Curve

"ROC for PSA, Underwood et al. 2012" : Current3
"ROC for PSA, Ferro et al., 2015" : Current3
"ROC for PSA, Ahn et al." : Current3
"ROC for PSA Thompson et al., 2005" : Current3
"ROC for PSA Jacobsen et al., 1996" : Current3
"ROC for PSA Etzioni et al., 2004" : Current3

ROC Curve

"ROC for PSA, Underwood et al. 2012" : Current3
True Positive Rate
"ROC for PSA Thompson et al., 2005" : Current3
"ROC for PSA, Ferro et al., 2015" : Current3
Reference Line
"ROC for PSA Jacobsen et al., 1996" : Current3

Figure 18 Empirical Receiver Operating Characteristic (ROC) curves for the PSA test

Disease Prevalence

The main and most important risk factor affecting all types of cancer, with the exception of cervical cancer, is getting older. Autopsy studies indicate that prevalence of prostate cancer is an increasing function of an individual's age (Jahn et al., 2015; Bell et al., 2015; Haas et al., 2008).

"If you take enough time to understand what this means, if I tell a patient, "Look I'm 47, my probability to have a prostate cancer histologically under the microscope right now as I sit here, is about 30%. Period." That's a start, so there's a pool of prostate cancer that we all carry, most of them they'll never become symptomatic, some of us have to have bad cards. Do we understand who have bad cards and who don't? No, we don't. There's a residual risk that there's something going on." — Peter Juni. MD-PhD, Director, Applied Health Research Centre, St. Michael's Hospital, and Professor of Medicine, University of Toronto, Previous: University of Bern, Director of the Institute of Primary Health Care, Professor and Chair of Primary Health Care and Clinical Epidemiology in the Faculty of Medicine, Switzerland

Since the real underlying prevalence of prostate cancer is unknown, we use estimates coming from autopsy studies conducted in different places. Figures 9a and 9b show the age versus prevalence relationship data for U.S. versus Mediterranean/Asian populations, and Figure 10c and 10d show the same relationship for U.S. black and U.S. white populations. U.S. black population has the highest prevalence whereas the Mediterranean/Asian population has the lowest prevalence. Autopsy data come from the following studies: Sakr et al., 1994 (Caucasian American, African American), Sakr et al., 1993 (U.S. white and U.S. black), Jahn et al., 2015 (U.S. black, U.S. white, Asian), Rebbeck and Haas, 2014 (European, Asian, African), Guileyardo, 1980 (U.S. white, U.S. black), Carter, 1990 (U.S., Japan), Yatani et al., 1988 (Japan), Stamatiou, 2006 (Greece), Soos et al., 2005 (Hungary), Sanchez-Chapado et al., 2003 (Spain). The black line gives model simulation for the age-prevalence relationship.

Sanchez-Chapado et al. ([2002]) gives the slope of the prevalence as 1.15 for Caucasian-American, 1.69 for African-American, and 0.91 for Caucasian-Mediterranean men; the model slope (Ω) for base case is a slightly more conservative value of 1.12. We assume that cancer prevalence starts from zero at the baseline age of Ψ, and then increases linearly with slope Ω (see Figures 10a, 10b). Figures 10c and 10d give available autopsy data estimates for U.S. black and U.S. white men.
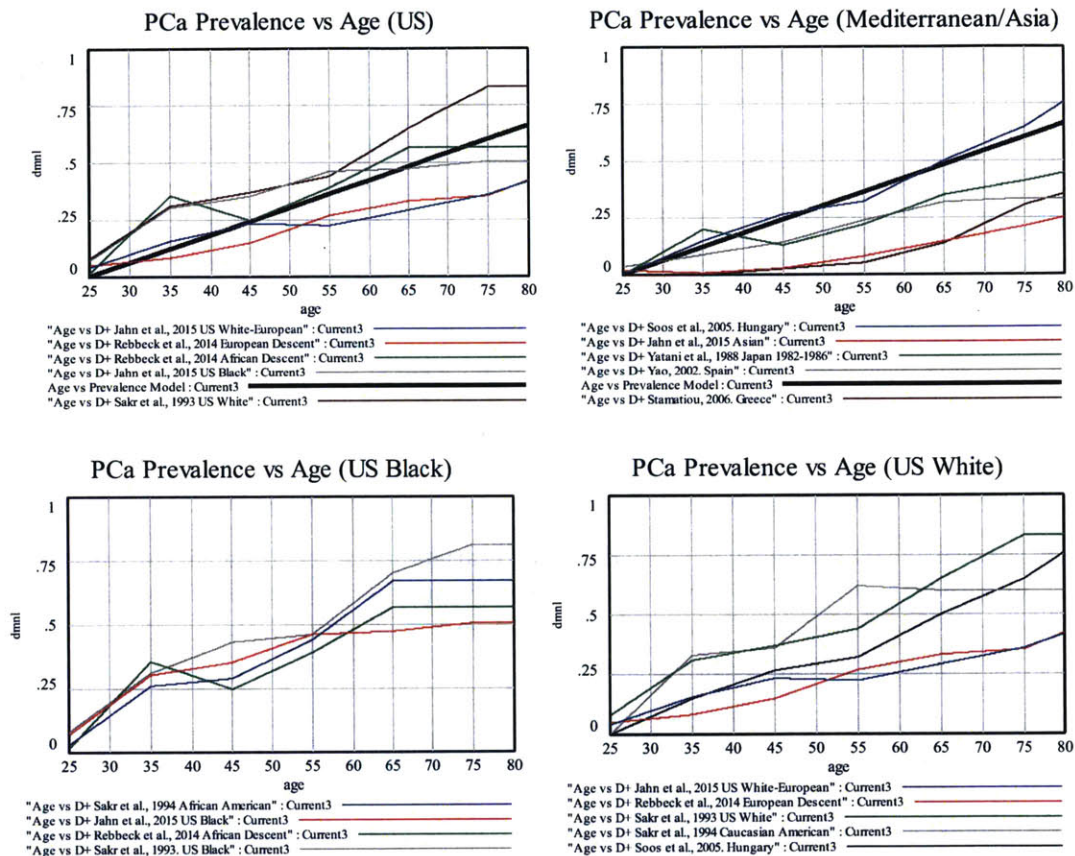
Figure 19 Age vs PCa prevalence data for a) U.S. b) Mediterranean/Asian c) U.S. white d) U.S. black

Unit Benefits and Harms Matrix

The balance of the potential health benefit and risk outcomes is critical for designing effective screening policies. The established balance may shift based on certain personal risk characteristics such as age, family history, or education level ([Cutler and Lleras Muney, 2010]). For example, potential health benefits and risks of PSA screening differ greatly in younger versus older men.

While there is a shift in balance at a personal level due to varying risk attitudes and individual preferences, the same shift in balance also occurs at the level of health institutions in the U.S. The difference in institutional priorities and values regarding routine screening is the main cause of the proliferation of screening guidelines available in the U.S.

"I mean, for an individual, they might say it doesn't matter to me. I just want to be safe. I don't care if it's unnecessary. I don't want the risk. I don't want to live with that risk....And people have trouble understanding just how big the risk is. I think any mention of cancer is scary, very scary." — Media, Science Reporter

"I hear a lot said about false positives and that they don't want to screen women because of false positives, and that for every, I think, 1900 women screened there will be 5 that are identified, one of which will ultimately be a breast cancer and 4 which will either get additional screening or biopsy, some people would say unnecessarily. But all the women that I speak to and I say that to say they would much rather go through a little anxiety, because that's the big excuse given I think, is that, "We don't want to cause these women undue anxiety." But I think women will tell you that they'd rather go through a little bit of anxiety and a biopsy or additional pictures, through mammogram or ultrasound or MRI, than go undetected. Because mortality's higher at late stage, and that's a fact." — Patient Advocate

"My mom was like, "It [insurance] covers it [mastectomy]," even though she had all these doubts she was, "It's probably better than I just get rid of the possibilities of getting cancer in the future," and she kept on reminding herself that because I guess she needed some justifications as to why this is good for her, so I think she kept on reminding herself with that." — Patient Relative

Results

Base Case Simulation— No variation in screening advice

In the base case scenario we assume that there is no variation in screening advice within the U.S., that is, all practitioners and their patients are complying with the recommendations derived from the evidence base. This is the most "ideal-world" setting one can imagine with regard to any population screening policy, as exemplified in this quote:

"I think it should be peer quantification of the harms and the benefits, and from authoritative panels. I'm not sure if the U.S. taskforce is that for the U.S. I think probably yes. There's politics involved, but I think nevertheless, I think we here in Europe should really believe in authoritative panels that are independent as possible and weigh the evidence that gets presented by the experts. I think that should be the situation. That should be the ideal situation." —Harry de Koning, Professor of Evaluation of Screening, CISNET comparative modeling group, PI of prostate cancer modeling group

There are two major time delays embedded in this policy structure: the modification delay for the recommended starting age R, and the evaluation and reporting delay to assess the benefits and harms of screening. Other decision-making delays include the adjustment time for the recommendation (λ), and the adjustment time for threshold value T (τ). The base case simulation serves for assessment of the effects of delays and nonlinearities inherent in the evaluation for screening advice.

Simulations confirm an overshoot in screening indications—similar to what we have observed in the 1990's-2000's in the U.S.—even if there is no variation in the underlying prevalence of the disease, in screening technology, or in harms and benefits. Harms exceed benefits as the target screening population is expanded, and we see damping oscillations until the HBR reaches its reference value of 1. Other variables (the age to start screening, population prevalence, and the threshold T) oscillate around a lower equilibrium.

The HBR is below its reference value at the start of the simulation, meaning screening has an added value compared to doing nothing at the beginning. Hence the threshold value and then the recommended and actual ages to start screening fall sharply within the next decade, which causes an overshoot in indications, and a quick expansion in the selection criteria. For screening to be effective target screening prevalence D^+ has to be high, and as prevalence decreases as a result of expansion of breadth indications, the actual harms come to exceed the benefits (the blue line). Note the phase lag between the actual and the perceived or reported HBR, which reflects the time needed to complete the evaluation process. When the benefit and harm evaluations finally reveal in the 2000's that the benefits of screening are lower than desired, policy makers gradually become more selective in their screening target population; that is, they narrow their selection criteria in order to improve future evaluations, and update their screening advice.

Indeed, the formal guidelines released by USPSTF in 2008 suggested that evidence was not sufficient to recommend PSA screening for men below 75, while the actual starting age for screening undershot the recommendation.
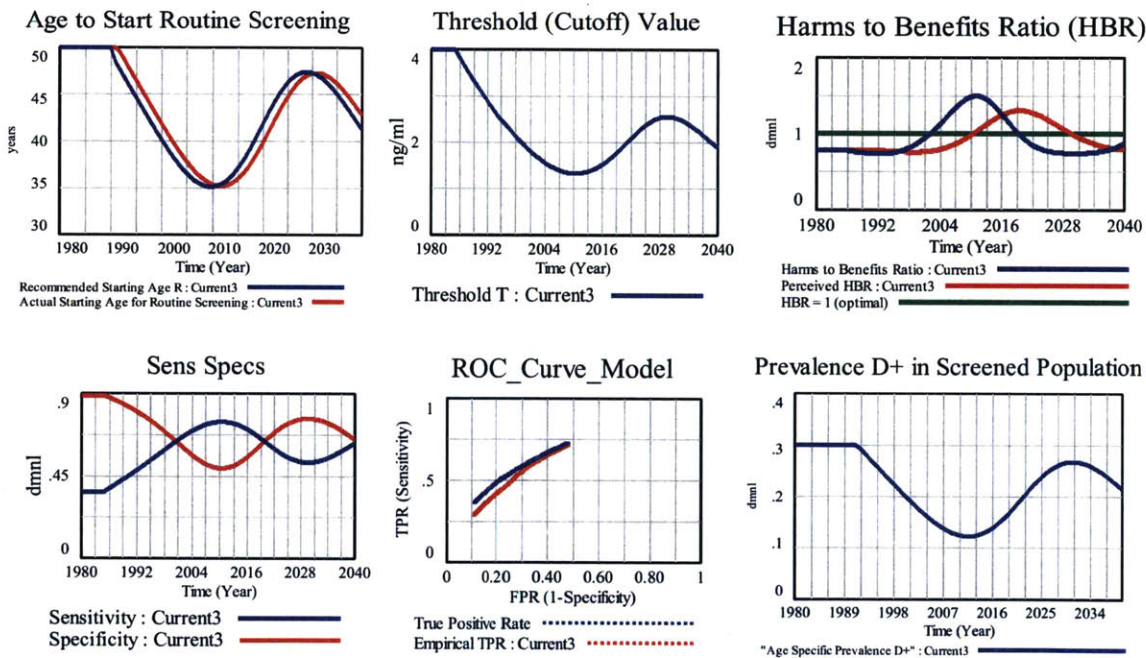
Figure 20 Simulations with base case parameter values

The policy structure we present corresponds to the ideal world: We assume that there is only one set of guidelines, which is perfectly followed by the public, and that the only consideration is the evidence-based harm/benefit calculations. In this perfect world we can gradually approach the optimal point for screening (HBR=1); yet note that even in this idealized situation we see an overshoot in breadth indications, which is a counterintuitive result. While the overshoot persists over a wide range of parameter values, the degree and extent of the overshoot changes with changing values of the model parameters. More specifically, the overshoot of indications gets amplified more when the Public Perception Delay (Φ) gets shorter, and the Time to Perceive HBR (γ) takes longer.

As practitioners and the public get more reactive to changing guidelines (the Time to Adjust R (λ) and Time to Adjust T (τ) get shorter), the amplification of breadth indications gets larger in either direction, or similarly when the evaluation and reporting of benefits and harms takes longer. Simulation results confirm that effective evaluation of the benefits and harms of screening is crucial, as well as correctly informing the public about the risks and benefits of screening, and not stampeding them to either direction.

Effect of HBR Translation Delay (γ) on Screening Recommendations:

Figure 12 shows the change in simulation results when the γ varies from 1 year to 20 years (baseline value=10 years). The HBR reaches its optimal value of 1 for a wide range of γ, yet screening becomes infeasible after a certain point as the γ gets longer and longer. For γ=20 years, harms of screening always exceed benefits and screening is not recommended anymore (see Figures 12c and 12d).
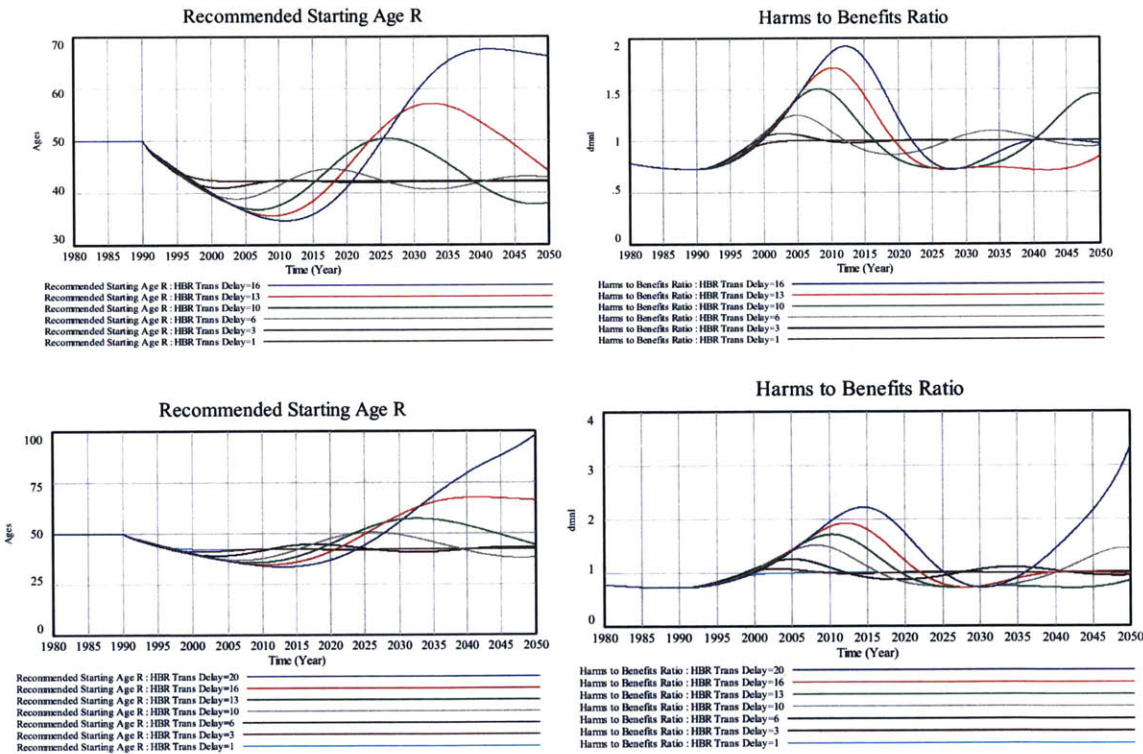
Figure 21 Effect of HBR Translation Delay on Screening Recommendations

Effect of HBR Multiplier ($\bar{a}$) on Screening Recommendations:

Figure 13 shows the effect of changing the HBR multiplier (α_{hbr}) on screening recommendations, as the α_{hbr} is varied from 0.1 to 1. This parameter indicates the strength of HBR evaluations on changing the breadth indications. As α_{hbr} gets higher, the overshoot in breadth indications gets amplified, and after a certain point, as it exceeds a certain value, screening becomes infeasible. For α_{hbr}=0.7, HBR evaluations override the "priming" effect of the actual practice, and screening is not recommended for any age group (see Figures 13e and 13f).
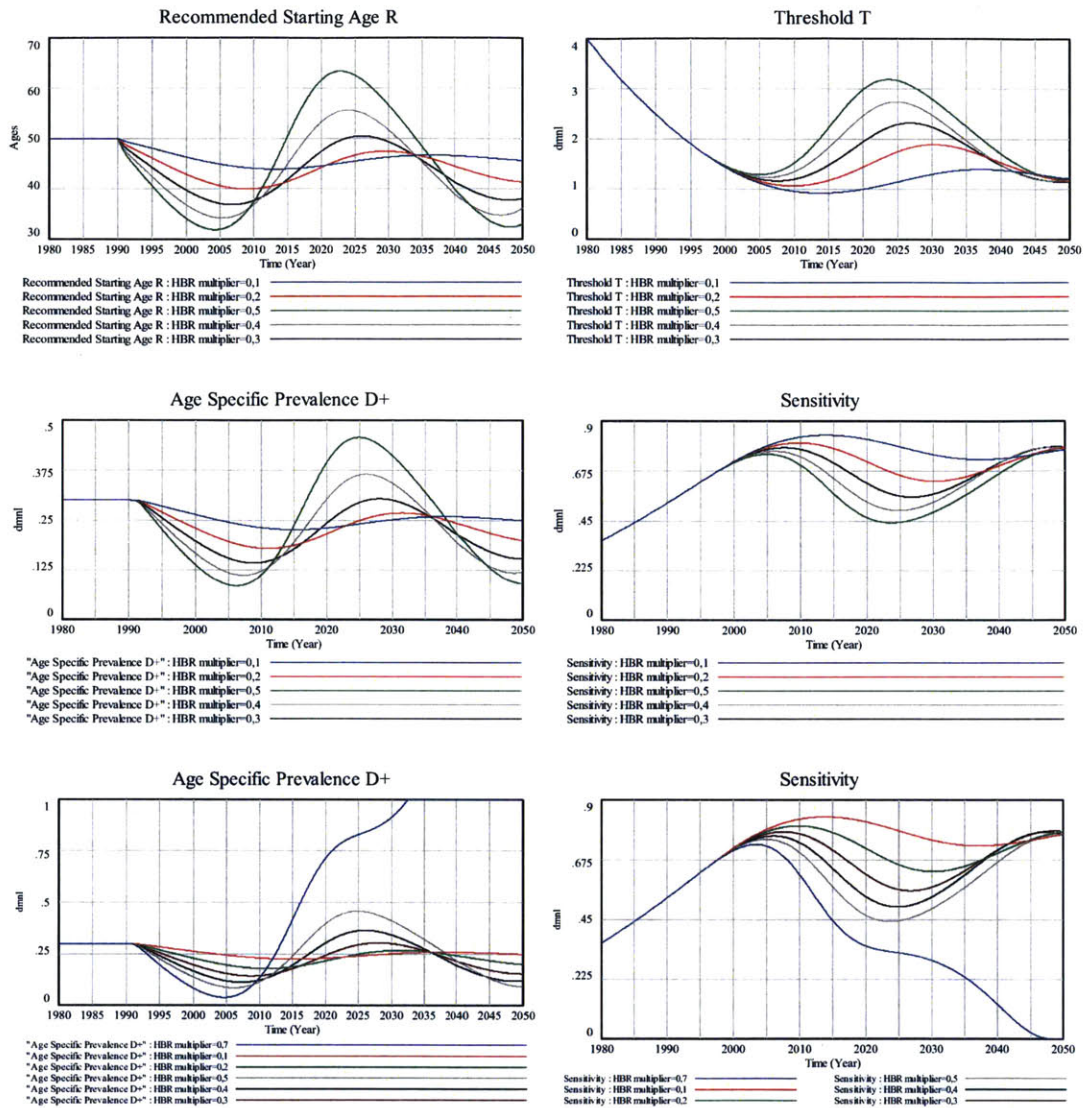
Figure 22 Effect of HBR Multiplier on Screening Recommendations

"Flipping the Coin": Simulation assuming test has no diagnostic validity

A screening test may only be feasible if its diagnostic accuracy is at least slightly better than just flipping a coin. We simulated this extreme condition, to test the model behavior, by overlapping the D+ and D- populations (see Figure 14a). The ROC curve falls exactly on the 45 degree indifference line and the AUC value becomes 0.5 as expected, indicating that no screening test can distinguish these two distributions from each other based on that particular test outcome alone (Figure 14b). The threshold T and recommended starting age to screen R reach unrealistically high values indicating the infeasibility of screening under this condition (Figure 14c).
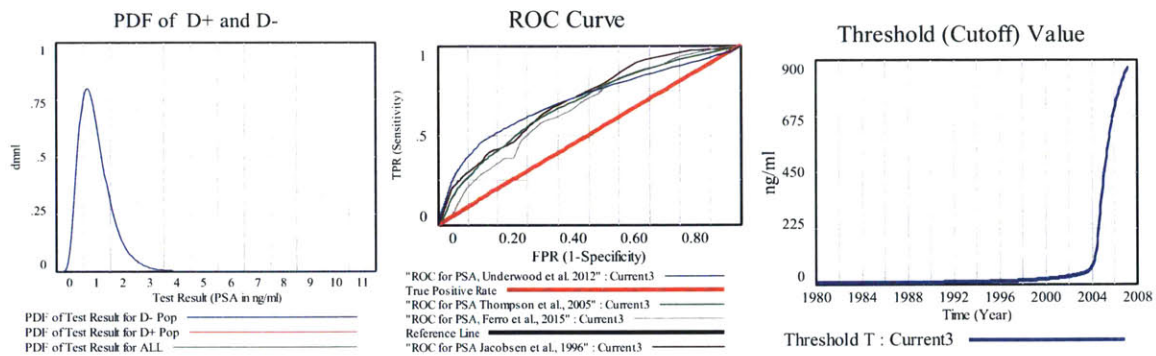
Figure 23 Simulation results for a hypothetical coin-flip test

Parameter Set Exploration

Several types of sensitivity tests are conducted on the model by exploring the parameter space. Monte Carlo simulation, also known as multivariate sensitivity simulation (MVSS), is used to automate the sensitivity analysis. In each of the cases below a subset of parameters is chosen to see how it changes the dynamic behavior of the model, given certain ranges.

Sensitivity to Translation and Public Perception Delays:

The HBR Translation Delay is varied between 2-15 years (baseline value=10 years) and Public Perception Delay is varied between 0.5-5 years (baseline value=2 years). Simulation results in Figure 15 reveal that oscillations persist in most situations, except in 5% of the simulations where harms exceed benefits, making screening infeasible.

We also conducted sensitivity tests by adding the two other time constants, the Time to Adjust T and Time to Adjust R, by varying them between 0.5-4 years (baseline value=1.5 years). For very short adjustment times the Recommended Starting Age R and the Threshold T get out of bounds.
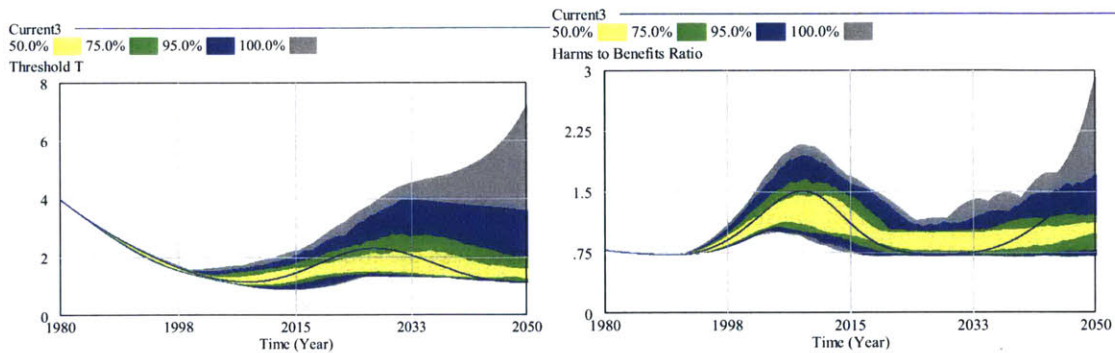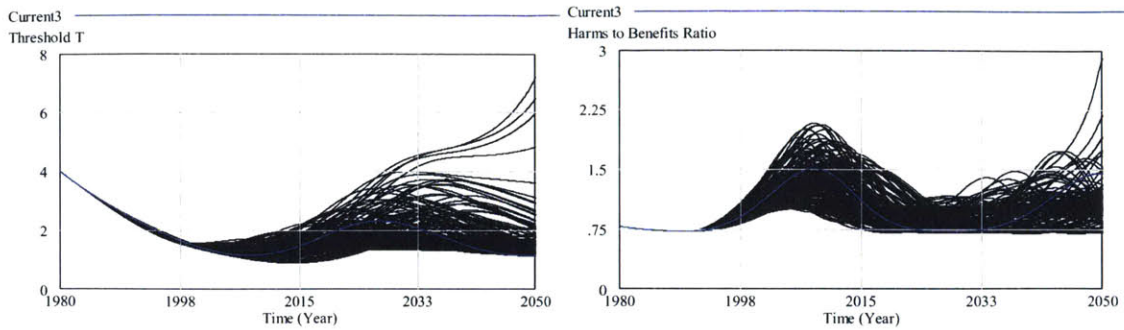
Figure 24 Effect of Translation and Public Perception Delays

Sensitivity to Changing Baseline Prevalence (A- Range: 0.05-5 and B- Range 0-1)

We conducted another set of simulations to test the model's behavior as the disease prevalence changes in the target screening population. To simulate the effect of constant disease prevalence, we varied the Baseline D^+ from zero to one, and the slope is made zero. D^+ equals to zero corresponds to the extreme case where no one in the population has the disease, and D^+ = one corresponds to the other extreme where everybody is sick with the disease.

Figure 16 shows the simulation results when D^+ is varied between 5 to 50%, and Figure 17 shows it varied between 0 and 100%. As the D^+ takes lower values, threshold T cycles around a higher value. Simulation results also indicate the existence of a plausible range for D^+ where screening is feasible.
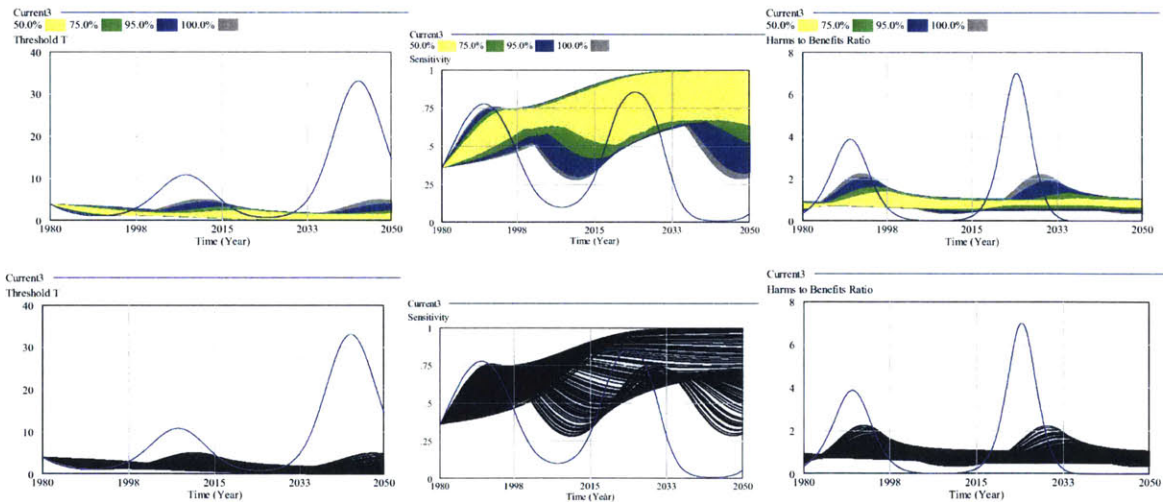
Figure 25 D^+ ranges between 5% and 50%

72
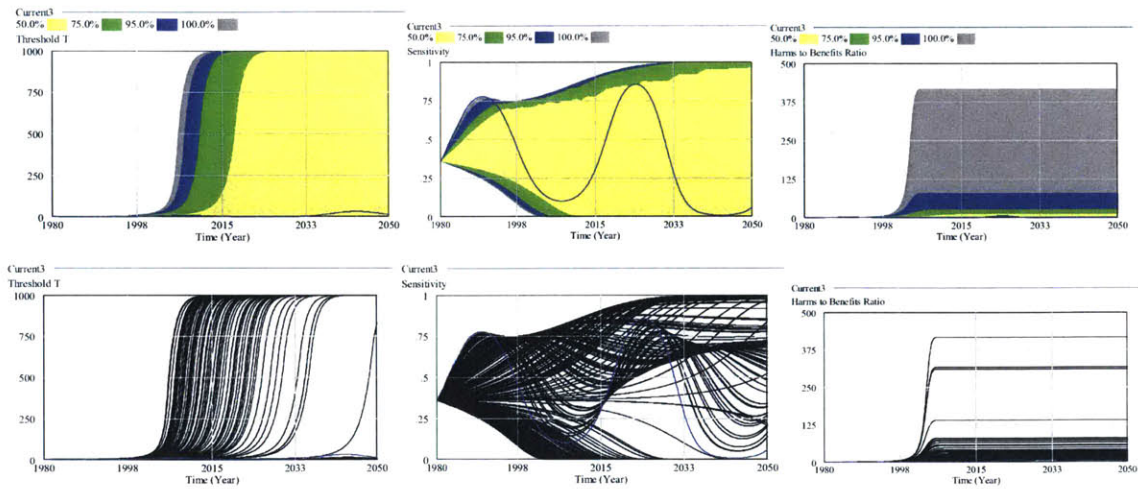
Figure 26 D⁺ ranges between 0% and 100%

Discussion, Implications, and Next Steps

Policy makers face a number of difficult choices and trade-offs in managing their screening recommendations and especially in dealing with the public reaction and resistance to updated recommendations. While clinical trials and empirical results provide the scientific evidence on which evidence-based screening recommendations are based, policy makers frequently employ various modeling techniques to fill in the gaps in scientific evidence that cannot be directly addressed by empirical evidence. Modeling studies are increasingly being used to guide screening policies. The U.S. Preventive Services Task Force (USPSTF) used modeling in developing its most recent breast (Mandelblatt et al., 2009) and colorectal cancer screening recommendations (Zauber et al., 2008).

Simulation models like ours can provide constructive insights and provide a dynamic intuition to supplement the typical empirical evidence for updating cancer screening recommendations, providing a formal means to improve the development and implementation of evidence-based screening and to moderate the public reaction against frequently changing recommendations. The resulting complex decision aid tool can be primarily used by healthcare professionals and policy makers.

Existing studies largely ignore feedbacks that condition the adoption of and adherence to guidelines. To our knowledge, this work represents the first attempt to explicitly model the decision behavior around health screening, including both the core issues and the environment in which the screening decision is embedded. We think that even a very stylized version of a dynamic model like that developed for the screening problem in this study can enhance rational decision making and improve the debate on screening policy by providing a decision aid tool for policy makers and practitioners. Lessons from this debate can be more generally applied to other contentious management and policy problems in which there is, at very substantial cost, a huge benefit for only a few and a small amount of harm for a larger number of people.

One advantage of a generic yet dynamically complex model is the simplicity of the core dynamic at work. It becomes possible to "feel" it more closely, as opposed to getting lost due to the numerical complexity associated with most resource allocation and optimization research. In our study most of the complexity comes from the structure of the system, that is, from the complexity of the intrinsic structure (delays and feedback structure). In real epidemiological studies in particular, or in real managerial applications in general, it is easy to lose this bigger outlook amid the numeric complexity of the underlying model. I do not argue that numeric complexity is unimportant in making real-life decisions. Rather, feedback-rich and structurally complex models can provide a simpler and larger dynamic perspective and a better means to aid intuition regarding real problems of concern.

The decision-theoretic model generates a dynamic pattern of the screening criteria that roughly matches the historical data. The PSA screening criteria have clearly expanded in the past 30 years and then narrowed, while showing little sign of rebalancing as the evidence base is ignored and overshadowed by patients, practitioners, and advocacy groups, going beyond the oscillations described in the core model. Simulation results reveal that perception and evaluation delays indeed play an important role in screening evaluations, and in the overshoot behavior of screening indications. The nonlinear feedback process and delays inherent in evidence-based screening aggravates the sub-optimality of screening guidelines. Although this study illustrates the "overshoot of indications" behavior for routine screening, other managerial applications may exist with similar potential behavior.
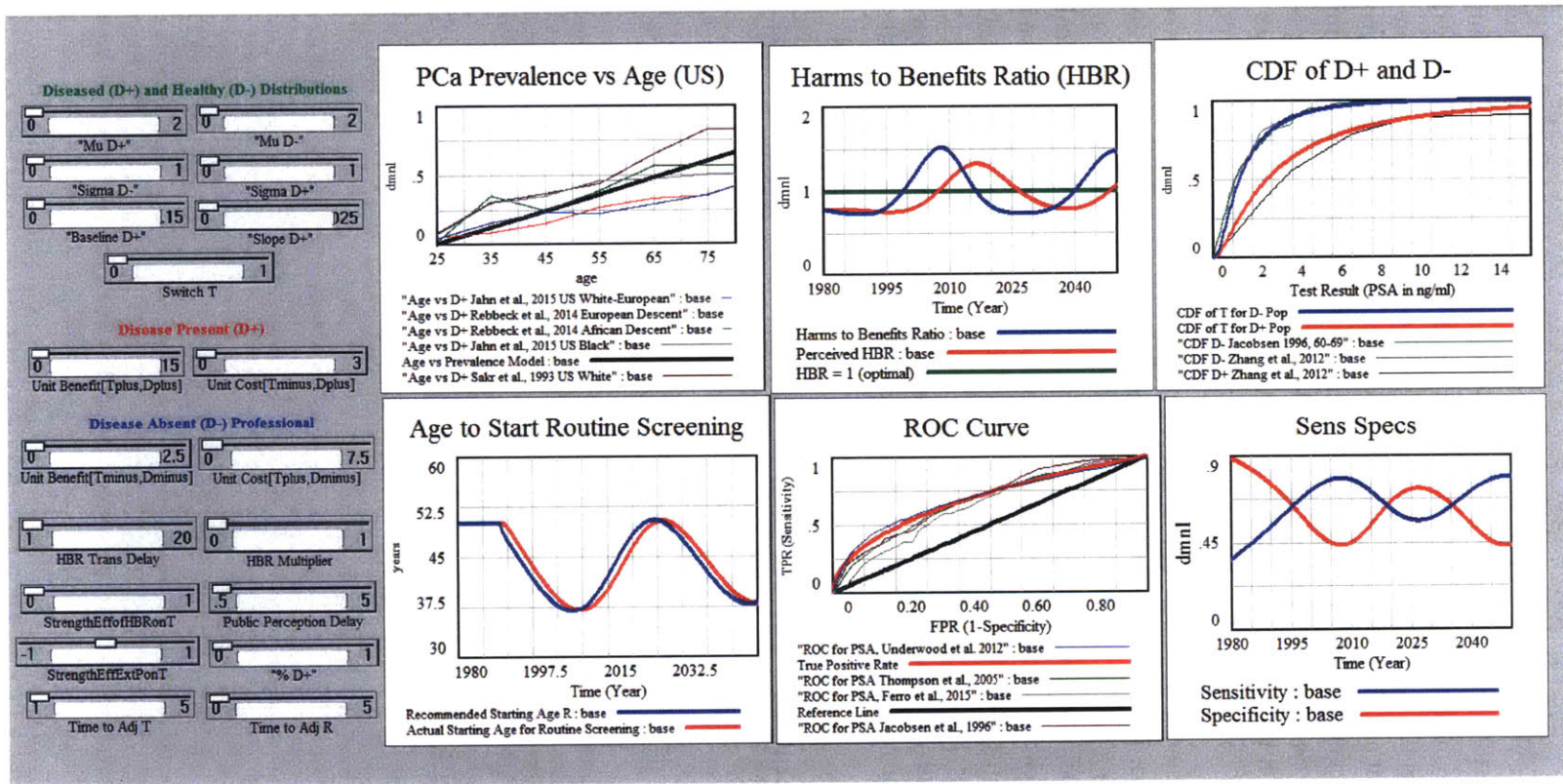
Figure 27 Model Dashboard

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Essay 3: A Dynamic Model for Understanding Long–Term Trends in Prostate Cancer Screening

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Abstract

Widespread population screening for disease remains controversial. Whereas guidelines for routine screening should be based on medical evidence, evidence often has relatively little impact on practice. This situation has led to ongoing controversy and conflict over appropriate guidelines among scientists, clinicians, and patient advocacy groups. There are significant variations in clinical practice, including evidence of over-screening for some diseases, and under-screening for others. To explain the patterns of over-/under-screening, fluctuating guidelines, low adherence to guidelines, and conflict between scientists and other groups, I develop the first explicit broad boundary feedback theory of the dynamics of medical screening, tested in a formal mathematical model. The model presents an extended case study specific to PSA screening for prostate cancer, including realistic presentations for the fundamental tradeoff between test sensitivity and specificity, the natural progression of the disease, and respective changes in population size and composition.

Keywords:

Health screening, evidence-based screening, population based screening, clinical practice guidelines, guideline development, disease (or policy) threshold, screening controversy, over-screening, computer simulation, system dynamics, medical decision-making, PSA screening

Introduction and Motivation

Clinical Practice Guidelines (CPG's) for routine screening such as prostate-specific antigen (PSA) testing or mammography have varied greatly in the United States, and often not been followed by clinicians and patients, with significant over-screening in some diseases and under-screening in others (Sirovich et al., 2003; Bleyer and Welch, 2012). Disagreement over the value of screening remains intense between evidence-based and advocacy/specialty groups, and how the evolving guidelines will translate into clinical practice is unclear. Evidence often has relatively low impact on practice and has led to ongoing controversy and conflict over the use of guidelines among scientists, clinicians, and patient advocacy groups.

After more than 25 years of widespread screening for prostate cancer, evidence-based professional groups in the U.S. have largely agreed that men should not routinely undergo PSA testing and should be informed that the test's harms may outweigh its benefits. The two biggest randomized trials, which came out in 2009, showed either minor or no benefit for PSA screening, and some of the formal guideline-issuing organizations reflected this in their recommendations. However, PSA screening rates in men of all ages didn't change between 2005 and 2010 (see Figure 1), and changed only moderately after the 2012 U.S Preventive Services Task Force (USPSTF) recommendation to stop screening for men of all ages. Goodwin (2013) suggests that "Neither the publication of the two large trials nor the subsequent changes in recommendations had an obvious effect on PSA screening rates".
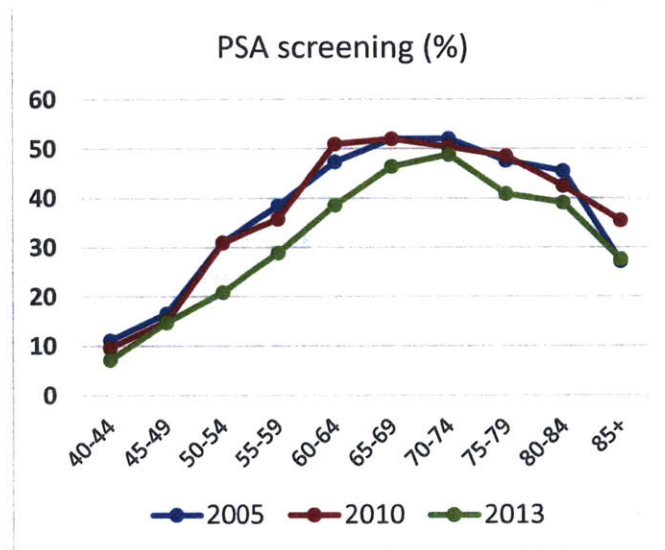
Figure 1 Proportion of men, by 5-year age group, who saw a physician in the year prior and received a prostate-specific antigen (PSA) test for screening purposes (Source: Drazer, 2015)

The motivation of this study is to develop a dynamic hypothesis to explain the underlying structure that accounts for fluctuations in criteria and over-screening, and why these are not corrected by evidence.

Dynamically complex policy problems have numerous characteristics that inhibit both the making and the implementation of effective policies, which necessitates endogenous perspectives. Yet existing studies either focus on the medical evidence supporting different screening guidelines or have not generally incorporated the broad boundary processes that condition the adoption of and adherence to evidence-based guidelines by clinicians, advocacy groups, and patients. A broad boundary framework is needed to support evidence-based guideline development (the policy formation) and to explain how screening criteria evolve over time. To our knowledge, this work represents the first attempt to explicitly model the decision behavior around health screening, including both the core issues and the environment in which the screening decision is embedded.

The PSA case study includes a natural history disease progression model for prostate cancer, and a behavioral theory explaining how guidelines change over time in response to changes in the evidence on the harms and benefits of screening. These in turn depend on the fundamental tradeoff between test sensitivity and specificity, on the natural progression of the disease, and on changes in population size and composition. We provide a simulation model of the decisions to alter guidelines for (a) the appropriate age for screening and (b) the threshold indicating a positive test result that includes the influence of common errors and biases in judgment and decision making and influences such as those of patient advocacy and clinician groups.

Background

System Dynamics Models for Health Screening and Cancer

The first attempt at a systems model of cancer was undertaken by Richmond in 1977. He developed a structural model of cancer that demonstrated how cancer develops (Richmond, 1977). Another study presents a systems theory of small-lung cancer (George and Taylor, 2006).

More recently, Fett built two system dynamics models to examine breast cancer screening for public health policy analysis. Fett et al. (1999; 2001) represents a model with multiple stages of breast cancer that could be used to examine the Australian breast cancer screening program. This study used the datasets coming from the Swedish Two County trial, which was conducted from the late 1970's to the late 1980's (also known as the landmark trial of mammography), and the Australian Breast Screening Program, a national program offering mammographic screening to all women aged 50-69 years.

There have been a few other system dynamics studies involving population health screening: chlamydia and cervical cancer screening (Royston et al., 1999); diabetes screening (Jones et al., 2006); and decision thresholds in developmental and behavioral screening (Sheldrick et al., 2013).

Royston et al. (1999) used system dynamics models to test alternative policies for cervical cancer and chlamydia screening. The U.K. Department of Health found the results to be useful for the development of screening guidelines. Policy questions included the optimal screening interval and coverage. The results suggest that it is more effective to increase the screening coverage than to decrease the screening interval. The model was later used to evaluate the effect of interventions aimed at increasing coverage.

Jones et al. (2006) summarize a system dynamics study of diabetes sponsored by the Centers for Disease Control and the Sustainability Institute in the U.S. More details of the model and the modeling process can be found in an earlier SD conference paper (Homer et al., 2004) on the same subject.

Most recently, Palma et al. (2015) built an SD model for prostate cancer that replicates the Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening trial with specific corrections for contamination and noncompliance. The objective of this model was to assess the benefits of PSA screening for prostate cancer-specific mortality.

Models for Prostate Cancer

The Cancer Intervention and Surveillance Modeling Network of the National Cancer Institute (CISNET) began their efforts in 2000 to project future trends and aid in the development of optimal cancer control strategies, comprising sites for breast, cervical, colorectal, esophagus, lung, and prostate cancers. CISNET models have a natural history disease model at their core. Interventions such as screening and treatment are then superimposed on the natural history model based on available evidence from randomized trials or assumed mechanisms of benefit (Etzioni et al., 2012).

The Prostate Working Group has developed and compared models of the natural progression of prostate cancer for over 10 years. The prostate models were originally developed to study the plausible effects of screening and changes in treatment on prostate cancer mortality (Etzioni et al., 2008; 2012). The models were then extended to reconcile widely disparate estimates of over-diagnosis associated with PSA screening (Draisma et al., 2009), to compare natural histories and risks of cancer progression (Gulati et al., 2011), to examine contamination in the prostate section of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial (Gulati et al., 2012), and to project expected disease trends under discontinued PSA screening (Gulati et al., 2014). Ongoing work is focused on assessing evidence of differential natural history in blacks and whites, and examining why mortality benefits differ in the PLCO cancer screening trial and the European Randomized Study of Screening for Prostate Cancer (ERSPC).

Modeling efforts to understand these patterns use data from autopsy studies, Surveillance, Epidemiology and End Results (SEER), the SEER Medicare-linked database, mortality data from the CDC, and population estimates from the U.S. Census Bureau. Studies of the incidence patterns estimated that approximately 29% of white males and 44% of black males were over-diagnosed, an important problem associated with the high prevalence of PSA-detected disease in older men that would not have progressed to symptomatic disease prior to death from other causes. Other findings concluded that if PSA screening was as effective as hypothesized in the major U.S. randomized screening trial, then it could be responsible for a huge portion, but not all, of the observed mortality decline.

For data collection I conducted an expert interview with the principal investigator of the Prostate Cancer Modeling Group, Professor Harry de Koning, who is a Professor of Evaluation of Screening, Biochemistry and Pharmacology. More information on the CISNET Prostate Cancer Modeling Group can be found at: http://cisnet.cancer.gov/prostate/index.html .

Research Methodology

This study uses a mix of quantitative/qualitative methods and a dynamic modeling approach to complex systems to explain the medical screening problem within the U.S. context (Forrester, 1961; Sterman, 2000). Modeling of prostate cancer in this project draws on an extensive body of system dynamics work on healthcare issues across various health disciplines (Homer and Hirsch, 2006; Homer, 2012; Hirsch et al., 2014; Milstein et al., 2012; Thompson et al., 2007; Tebbens et al., 2005; Dangerfield et al., 2001; Sterman, 2006; Karanfil and Barlas, 2008; Rahmandad, 2014).

The problems around cancer screening are particularly suited to SD modeling because of the presence of many time-related phenomena, delayed feedback and nonlinearities, such as varying trends in screening dissemination and population structure, and the delays associated with translation of evidence and policy-making efforts. SD methodology employs a series of guidelines for the model building process (Randers, 1980; Wolstenholme, 1990; Sterman, 2000), and a variety of tests and types of evidence. These are organized around the purpose of the model, and serve to increase the confidence in model structure and to support the hypothesized dynamic theory (Forrester and Senge, 1980; Barlas, 1996; Sterman, 2000; Rahmandad and Sterman, 2012, Martinez-Moyano, 2012; Homer, 2014).

Overview of the PSA Screening SD Model (PSA-SD)

In Essay#2 I presented a generic model to explore and formalize the guideline formation process in population screening. I started with a small policy structure and then embellished it gradually, adding one layer at a time while testing the model structure and its outputs throughout this process.

Now we are expanding the boundaries of this classical evidence-based model (the Core Model) to create a more realistic life setting, including the influence of the political environment in which the actual screening decision is embedded. More specifically, we will look at how medical professional societies—including radiologists, patients and patient advocacy groups, and other principal actors—influence the adoption and diffusion dynamics of medical screening in the U.S. context.

The "Core Model" provides the foundation for the development of evidence-based screening guidelines. The "Model of Actual Practice" extends and integrates the "Core Model" with the "Interpretation and Implementation of Formal Guidelines." These will then be tied to a natural history model for prostate cancer that simulates the population-level changes in screening, dissemination, and treatment.

The main structure and equations for the evidence-based model, implementation and the actual practice are explained in Essay#2. The same structure is now subscripted by different groups to represent the different roles played by professionals (evidence-based actors such as the USPSTF and the ACS) and the advocates (including most patients and patient advocacy groups, laypersons, and medical specialty groups).

The range of screening indications in the model include the biopsy threshold and the recommended starting age, which are now subscripted by group. The effective biopsy threshold emerges as the weighted average between the two thresholds suggested by professional and advocacy groups,

where the weight implies the doctors' weight put on evidence-based recommendations. Similarly, the actual starting age for screening emerges as the weighted average between the advocacy and professional group recommendations, depending on how much weight the public puts on each of these.

Our extended model for the PSA case study will be grounded in empirical evidence. A mix of qualitative/quantitative methods will be used to explain the dynamic nature of the population-level health-screening problem. While the screening debate is not specific to the United States, we mainly treat the problem within the U.S. context.

Data Types and Sources

Data used in this study are from multiple sources. Some are secondary data based on literature, such as medical articles and reports we accessed directly. Others are composite data, which we obtained from combining several data points to support the model design. The majority of historical population and prostate cancer trends are widely available on organization websites such as NCI, CDC, NHANES, U.S. mortality files by the National Center for Health Statistics, NCI-SEER database, and NHIS. Complementary data were gathered from a literature review of the history of PSA screening in the U.S. As noted above, the focus is on a 60-year period, from 1980 to 2040, that includes a portion of the pre-PSA era. To bring the model assumptions and findings closer to the real trends and to support the emerging dynamic hypothesis, we collected additional data through interviews with domain experts in screening or cancer.

Model Boundary

Figure 2 presents the boundary of the extended model, indicating the endogenous variables modeled thoroughly and less thoroughly, exogenous variables for which parameters or time series are used as an input for the simulation time horizon, and other variables which are intentionally left outside of the system as they are unrelated to the problem of concern (Ford, 1999). The model boundary is comprehensive enough to capture the causal mechanisms that drive the system behavior (Forrester, 1987).

Please note that some of the variables previously listed as exogenous, or outside of the model boundary in Essay#2, are now either endogenized, or made exogenous. These include screening dissemination variables, clinical detection, biopsy, treatment, population increase and aging, weight put on evidence-based recommendations, and harm reduction technology.

Change in
Treatment
Effectiveness

Optimal Screening
Schemes

PSA Distributions
of D+ and D-

New
Biomarkers

Adjustment
Delays

Population
Structure

Recommended
Starting Age for
Screening

Threshold

Risk Perception

Weight of
Evidence

Health System
Changes

Genetic
Testing

Clinical
Detection

Sensitivity/
Specificity

Screening
Dissemination

Popn
Increase

Prevalence of
Target Population

Harm and
Benefit Ratio

Weight on
Recommen
dations

Medical Ethics

Harm Reduction
Technology

Biopsy

Aging

Treatment

New
Technologies

Bias

Endogenous

Evaluation and
Dissemination
Delays

Underlying Real
Disease
Prevalence

Informed
Consent

Exogenous

Patient-provider
relationship

Outside of Model
Boundary

Figure 2 Bull's-Eye Diagram for the PSA Case Study

Main Feedback Loops

A high-level overview of the causal structure of the model is presented in Figures 3 and 4. Five indicators are of main importance: biopsy threshold, starting age to screen, cancer survivors, over-diagnosis, and perceived harms and benefits. The CLD in Figure 3 provides an overview of the three main balancing feedback loops that drive the evidence-based guidelines.

B1-B2) Evidence-based correction: These are the core feedbacks responsible for setting guidelines using the classical approach to find an evidence-based balance. For screening, these relate to sensitivity and specificity of screening, and a cost-benefit analysis. This is the first step in decision making; it only involves "available facts" and the analysis of evidence. For PSA screening, these facts include a description of the available options (screening or no screening), the possible outcomes of those options (biopsy and downstream treatment if tested positive, cases of cancer diagnosed, lives extended, the effort of screening and workups, the effect of false-positive results), and the chances that any of these outcomes may occur. Loops B1 and B2 show how potential harms and benefits of screening change the scientific evidence base and how a natural balance can be established after a harms and benefits evaluation.

B3) Harm reduction technology: Mitigating feedback coming from new or improved technology emerging in response to side effects of treatments is an important and systematic balancing process in medicine. It is one reason that in the 1970's the U.S. Office of Technology Assessment wrote about the "moving target effect" complicating definitive assessment in medicine. New technologies emerging in response to side effects causes a decrease in the harms/benefits ratio, eventually leading more people to be treated for the disease, which is termed the "treatment expansion effect."

The effect of treatment expansion is that doctors tend to diagnose the disease more frequently when treatments are safer and easier to tolerate, and patients pay more attention to their condition when treatment is more effective (Cutler and McClellan, 2012). For example, the rates of surgery for prostate cancer surged in the 1980's after the development of nerve-sparing techniques for radical prostatectomy (Etzioni et al., 2012).
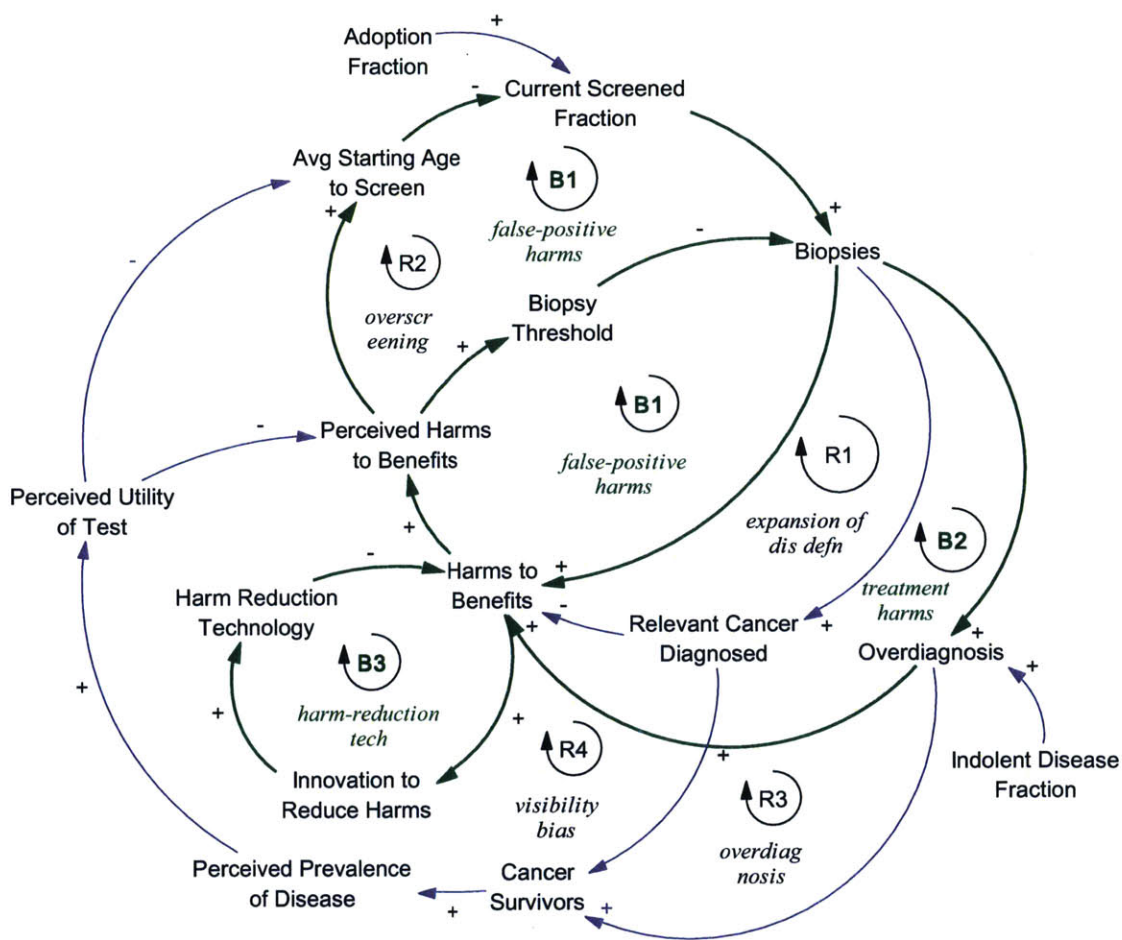
Figure 3 Screening Causal Loop Diagram- Balancing Loops

The CLD in Figure 4 provides an overview of the four main reinforcing feedback loops that drive the cascade for over-screening/over-diagnosis and over-treatment for cancer:

R1: Expansion of disease definition/Finding and redefining disease: A potential decrease in the biopsy threshold increases the number of relevant cases diagnosed early, and (under favorable assumptions) finding relevant cases early decreases the harms to benefits ratio, which leads to a further decrease in the biopsy threshold. This means an expansion in disease definition, and hence expansion in breadth selection criteria. Adoption of new disease definitions is shown to exist for various conditions including hypertension, hypercholesterolemia, and being overweight, and it can dramatically increase the disease prevalence (Schwartz and Woloshin, 1999). For prostate screening, the proportion of the population affected by different thresholds varies with age. Welch et al. (2005) finds that lowering the PSA threshold to 2.5 ng/ml doubles the number of men defined as abnormal.
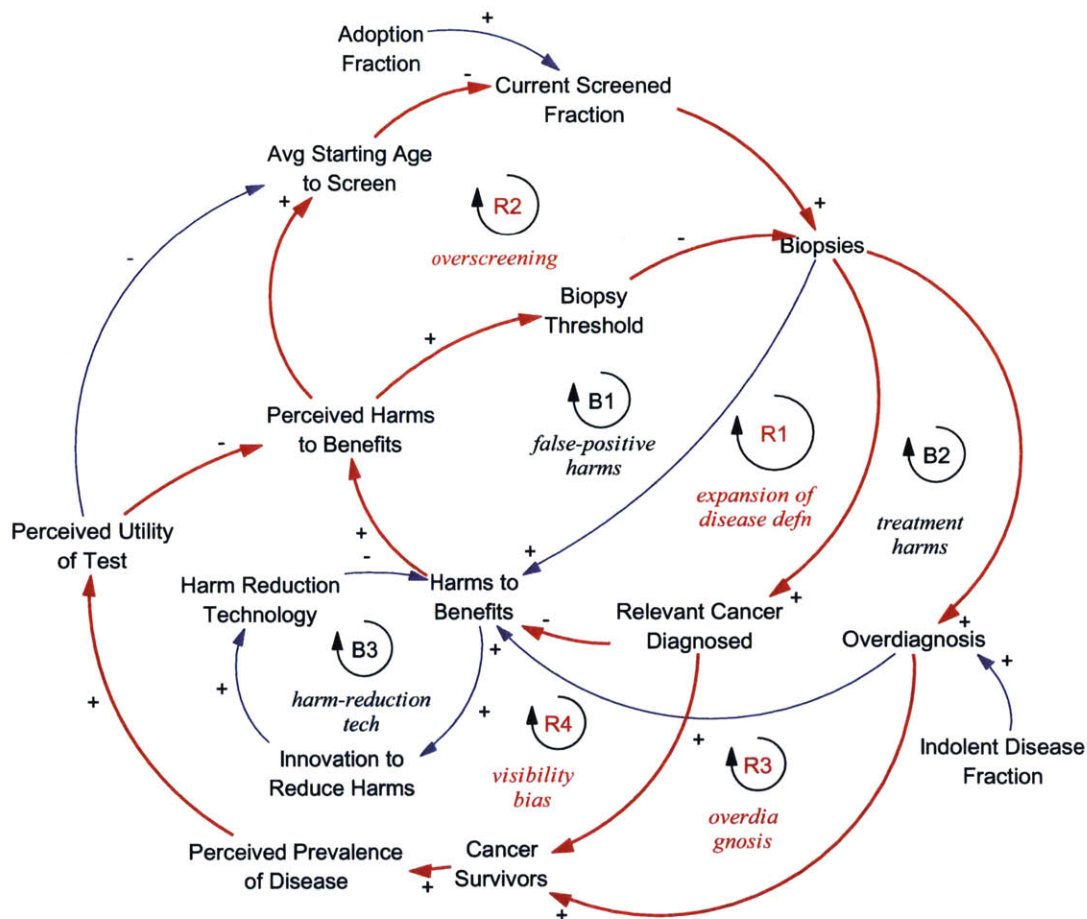
Figure 4 Screening Causal Loop Diagram- Reinforcing Loops

R2-R3) Over-screening/Over-diagnosis/Overtreatment/Cancer Survivors: More diagnosis in turn creates the potential for labeling and detection of pseudo-disease—disease that would not have become apparent to patients during their lifetime without testing (Fisher and Welch, 1999.)

As more and more men are given a cancer diagnosis by screening, the natural perception of each "survivor" is that screening "saved" his life. However a portion of these survivors have a type of prostate cancer that could have been treated as effectively when found later, or that might not have

caused problems. The problem is that for each "survivor," there is no way to know whether screening and the treatment "caused" survival, as there is no counterfactual. Thus, the number of men who perceive benefit from screening is substantially greater than the number who actually receive benefit, and the impression of benefit is exaggerated. Numbers are increasing as more men undergo treatment for prostate cancer. Over-diagnosis and cancer survivors were a big part of the interview data:

Over-screening: *"PSA is overused because, first, no one wants to be blamed for missing a possible prostate cancer diagnosis, and second, most of the patients are asking for it. Additionally, we also know that PSA is not specific for prostate cancer and it can be increased in other prostatic diseases such as benign prostate hyperplasia or prostatitis. — Ilker Tinay, MD, Urology, Marmara University School of Medicine, Previous: Brigham and Women's Hospital, Urology*

Overdiagnosis: *"If you have breast cancer you want to get the best treatment, which is most likely to cure you. Currently the chance of cure is closely linked to the size of the cancer at presentation. For example, less than 2 cm breast cancers, without spread to the lymph nodes, have cure rates over 90%, on the other hand cancers that are 5 cm or larger or have multiple lymph nodes affected can have cure rates below 50% .." Which group you would like to be? Obviously, if you can do something about it, you want to have the smallest possible cancer. This is where mammographic screening can help. The down side, we increasingly recognize that some mammographically identified cancers are cancers in name, and appearance, only. They would not harm or shorten the life of a person even if left untreated. This is called over-diagnosis. The extent of over-diagnosis, that is what faction of cancers picked up by mammogram would have not harm an individual, is intensely debated." —Lajos Pusztai, Yale School of Medicine, Chief of Breast Medical Oncology, Co-Director of the Yale Cancer Center Genetics and Genomics Program*

Overtreatment: *"I also think the entire area of overtreatment is critical and I think our feelings about it are spurred by a gut reaction to get the cancer out. I think the issue of overtreatment is a much bigger issue than we give it credit for. I understand viscerally and I understand as an early-stage patient that desire to cut as much as necessary to make it go away. I'm the perfect example of how that doesn't work. — Patient Advocate*

Cancer survivors: *"We all know cases where people would not have had their disease detected if they hadn't been screened early. It's not necessarily proven that they would not have survived without that screening. We can't know that for an individual, and studies of many individuals can be misleading because of biases like lead time bias and length bias. What many people respond to, however, are anecdotes. You hear about a women whose breast cancer was detected by mammography in her 30s or 40s, or PSA in a younger man that can seem pretty compelling. And anecdotes are really powerful, in fact we learn a lot from anecdotes and anecdotes are really important. But they're only one small piece of evidence and not usually the most useful piece of evidence. I think anecdotes drive some screening that's not necessarily warranted..."— Matt Gillman, M.D., S.M. Director, Environmental Influences on Child Health Outcomes (ECHO); Office of the Director, National Institutes of Health[3]*

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[3] Prof. Gillman provided input while he was professor of population medicine at Harvard Medical School and a member of the USPSTF. He is now director of the NIH program Environmental Influences on Child Health Outcomes. The views he expresses are his own.

R4) Visibility Bias: The last layer of feedback represents a separate set of feedback dynamics that affects the average person's perception of harms and benefits from screening. The interview data suggests that the opinions of professionals and advocacy groups diverge substantially when it comes to perceived harms and benefits. Evidence-based groups generally consider over-diagnosis and over-treatment as the most important harms:

"The most important harms [of screening] are really over-diagnosis and over-treatment. Those are basically the most important ones. To get a good schedule on that is crucial" —Harry de Koning, Professor of Evaluation of Screening, Biochemistry and Pharmacology, CISNET modeling group

Advocacy groups and laypeople, on the other hand, draw on a different set of factors to form an opinion about screening, and have other priorities. Using a cross-sectional survey, Schwartz and Woloshin (2000) show that "Women are aware of false positives and seem to view them as an acceptable consequence of screening mammography. In contrast, most women are unaware that screening can detect cancers that may never progress but feel that such information would be relevant." Patients and patient advocacy groups see false positive test results and anxiety as the main drawback of screening, and they usually do not take it into account while making decisions:

"I don't have the data on this, but I think that from speaking to women themselves, I think that, yes, when you talk about the drawbacks and benefits of screenings, women are much more afraid of a cancer that is undiagnosed than of having a screening and having the biopsy. You know, I'd rather have that knowledge and have that control.... And once I do wind up with a cancer, and it's not—and I could have caught it earlier. So it's the same thing, when they choose to have a mastectomy versus a lumpectomy that many of them don't want the anxiety of having to go back for all these screenings and having to worry. They'd rather just know they did everything they could to get rid of every breast cell they have in their body as much as they could. — Deborah Kotz, Press Officer at FDA

Description of the PSA Model

This chapter describes the extended case study model for PSA screening, which consists of six fundamental sectors including the population and natural history of disease; screening and clinical detection; treatment; screening dissemination; harm reduction technology; and the PSA screening harms and benefits. The fundamental approach and assumptions for each sector will be explained with critical formulations. Pictured in Figure 5 is the conceptual framework used for modeling prostate cancer natural history, screening, adoption, utilization, harms, and benefits. The various assumptions and propositions are supported by reference to the modeling and medical literature discussed earlier. The chapter concludes by listing important model parameters with information sources.
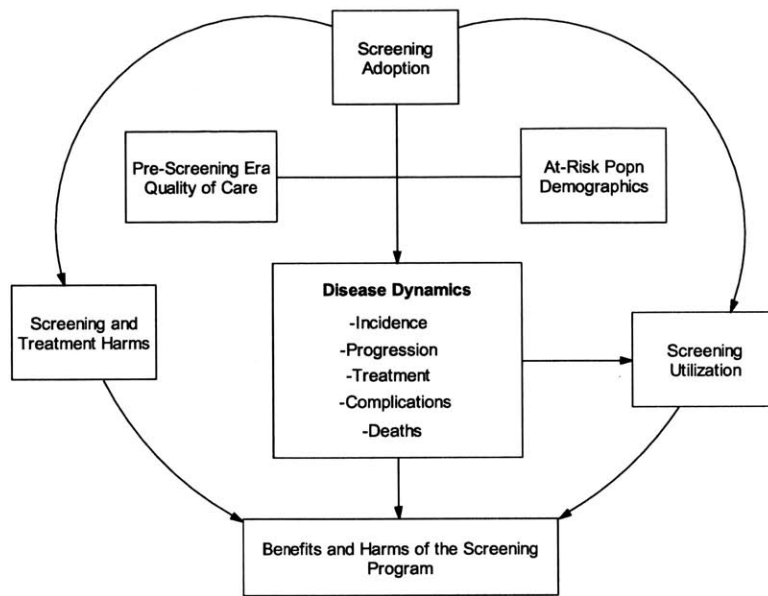
Figure 5 Framework for modeling of PSA screening for prostate cancer (adapted from <u>Homer et al. 2004</u>)

Population and Natural History of Disease

Population Increase and Aging:

The target population of interest is U.S. male (all races) 50-80-year-olds; however, we also model younger ages (35-50-year-olds) to improve the quality of model calibration to target population trends. We define nine age groups by five-year intervals starting from 35, and another age group that represents the 80+ male population.

Different age groupings are used to represent simulation results, including the most commonly used 50+ or 65+ populations. Other subpopulations include the 35 to 44, 45 to 54, 55 to 64, 65 to 75, and 75+ year-old age groups, for which mortality data and population counts were made available by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC) (<u>Compressed Mortality File</u> Link).

The aging structure comprises one inflow (age$_i$enter) that indicates the rate of entering for the indicated age category, for 9 age groups, and one outflow (age$_i$leave) that indicates the rate of leaving the age category. The inflow-of-male-population-turning-35 time series is provided exogenously for the years 1980-2040, based on U.S. Census data history and future projections:

$$age_{i+1}^{enter} = age_i^{leave} \quad \text{for i=1, 2... 9, else 0 for} \qquad \text{i=0}$$

(1)

The age cohort-specific all-cause death rates, and projections for the decrease in all-cause-mortality were derived from sex- and age-specific <u>U.S. Life Tables</u>. The all-cause death rates for all age groups are then compared to the death counts specified by the CDC WONDER-<u>Compressed mortality file</u>.

90

Net Immigration (migration to and from a country) is another component that influences the historical and future population counts in the U.S. This study uses the U.S. Census Bureau past data and projections for immigration as an input time series, as a certain fraction of the population that ranges between 0.001 and 0.0049 for the simulated time horizon of 1980-2040. Data were not available by age group (U.S. Census, 2011). Cumulative net migration between 1980 and 2040 accounts for over 11 million people in the base case simulation for the 35+ U.S. male population.

Natural History of Disease:

Figure 6 illustrates the natural history of prostate cancer and its diagnosis, including the health states and transitions, the asymptomatic onset of screen-detectable cancer, and disease progression through stages. The model design (onset and progression through disease stages) and assumptions were inspired by the prostate cancer natural history diagnosis and history models developed by the Cancer Intervention and Surveillance Modeling (CISNET) research group and other modeling studies published previously (Cowen et al., 1994; Etzioni et al., 1998; Etzioni et al., 1999; Tsodikov et al., 2006; Gulati et al., 2010).

In this model, screen-detectable cancers progress from loco-regional (M0) to distant-metastatic stage (M1). Cancers are localized at onset and may be either low-grade (Gleason score 2-7), high-grade (Gleason score 8-10), or indolent (any Gleason). High- and low-grade cancers represent those which are of progressive type and may get metastasized, while the indolent class tumors represent the non-progressive, or latent tumors, including regressive tumors which are, by definition, destined to stay confined to the prostate and not metastasize or kill the patient. The model assumes stage durations to be distributed independently according to exponential distributions and not correlated with each other. The disease progression rates are independent of patient age or disease onset, as with other studies. The model also assumes that indolent and progressive tumors cannot be distinguished at diagnosis and will be treated similarly.

Finding an indolent cancer is not necessarily harmful. However, because there is no way to definitively distinguish an indolent cancer from a progressive one, most screen-detected cancers are treated aggressively with radical prostatectomy and/or radiation therapy. While there is an increasing trend to treat loco-regional cancer with watchful waiting, men are usually dissatisfied with it, as it provides only palliative therapy if cancer progresses (Hoffman, 2010).

Asymptomatic onset used in the model (Ox_i) is estimated from autopsy studies and previously published models (Jahn et al., 2014; Sanchez Chapado et al., 2002; Bell et al., 2015; Cowen et al., 1994; Bubendorf et al., 2000; Underwood et al., 2012). This model assumes that these adequately reflect the real prevalence of disease in the U.S, although that may be an underestimation of the true amount of latent disease in the population. Biopsy studies using better techniques find higher age-specific prevalences. The present model assumes a constant secular trend in incidence, in line with other modeling studies. The probabilities of tumor grade at onset (p_j^{Ox}) determine the fraction of disease in each grade category (high, low, indolent) at onset, and add up to one. The equation for the asymptomatic incidence rate (asxInci) is given below:

$$asxInci = AtRisk_i * Ox_i * p_j^{Ox} \qquad (2)$$

The metastasis hazard for men with cancer depends on grade, and the hazard of transition to metastatic disease from loco-regional to distant stage (Mx) is selected based on literature review (Ghani et al., 2005; Scardino et al., 1994; Underwood et al., 2012). The metastasis rate (mx) from loco-regional to distant disease is given by the following equation:

$$mxM0 = UxM0_{i,j} * Mx_j * M_s \qquad (3)$$

Mortality of prostate cancer from loco-regional and distant disease stages is represented with death fractions defined by grade (df_j^{M0} and df_j^{M1}). The death fraction and metastasis hazard of indolent tumors are zero by definition.

A comparison of high-level features across different CISNET models and this model (PSA-SD) is presented in Table 1 below. Important parameters are listed in Table 2, at the end of this section.

Table 5 Comparison of high-level features across models (modified from Gulati et al., 2011)

MODEL FEATURE	FHCRC	MISCAN	UMICH	PSASD
Implementation	Simulation	Simulation	Analytic	Simulation
Disease States	(2 stages)x(2 grades) Loco-regional, distant stage Low-moderate, high grade	(3x 2 stages)x(3 grades) T0-T3 local, distant stage Low, moderate, high grade	(2 stages)x(2 grades) Loco-regional, distant stage Low-moderate, high grade	(2 stages)x(3 grades) Loco-regional, distant stage High, low, indolent grade
Progression depends on	Current PSA level	Current disease state	Delay time and mode of detection	Current disease state and delay time
Stage progression	Yes	Yes	Yes	Yes
Grade progression	No	Yes	Yes	No
PSA test sensitivity	Output of model	Endogenous parameter	Endogenous parameter	Endogenous
Biopsy compliance	Estimated from PLCO	Combined with PSA sensitivity	Combined with PSA sensitivity	Based on lit review
Biopsy sensitivity	Based on lit review	Combined with PSA sensitivity	Combined with PSA sensitivity	Based on lit review

Natural history model has 2 stages, locoregional and distant (M0 and M1), and 3 grades (1=High grade, 2=Low grade, 3=Indolent)

Ux Undiagnosed, Sx Detected by PSA Screening, Cx Detected Clinically
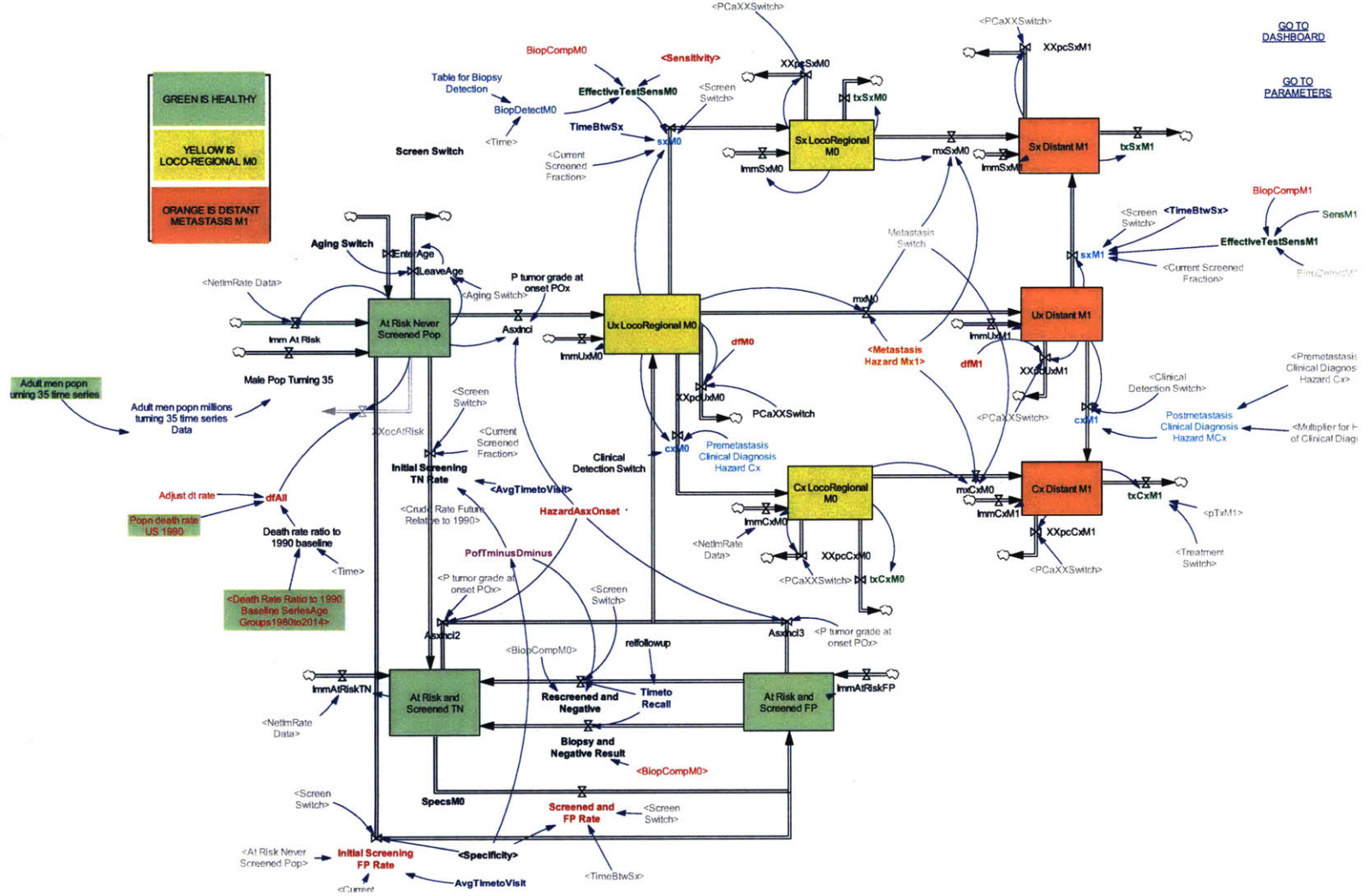
Figure 6 Natural Disease Progression, Screen- and Clinical Detection Secto

Screening and Clinical Detection

PSA screening and biopsy follow-up:

Existing studies generally superimpose population screening and biopsy patterns on the underlying disease progression process, using screen rates based on Mariotto et al. (2007). The model in this study endogenizes the adoption and diffusion of the screening process, and defines the different components of screen detection explicitly. These include the fraction of population that receives the screening test, sensitivity of the test, biopsy compliance, and biopsy detection. Test sensitivity and current screened fraction are endogenous to the model, while biopsy compliance and detection are exogenous.

Subjects are eligible to receive regular screenings if their doctor adopted the PSA screening test at the time, and if they are around the age-eligible range for the test. Interview results confirm that one of the main determinants of screening is the doctor's opinion:

"Access to care, coverage, and I also think it is how the screening is presented by their doctor. I think a lot of medicine is sales, and if a doctor presents something as either optional or a bad idea like, "You don't really want to do that, do you?" the patient's going to say no. But if their doctor's enthusiastic about it and believes in it, then they're probably more likely to go ahead and get it done…" — MD, PhD Erin Hofstatter, Medical Oncologist

Subjects who are at risk and never screened may get an initial screening test with a true negative test result or a false positive test result. The subjects with a false positive test result may then have a follow-up test, or get a biopsy to confirm that they do not have the disease. Existing modeling studies do not explicitly define these population stocks of people with a true negative or a false positive test result. In this study we use the flexibility of the system dynamics modeling stock-flow structure and add these stocks to keep track of their values. The value of the false positive stock relative to the healthy population may be an important indicator for policy making.

Subjects in all the three at-risk stocks (at-risk never screened, screened TN, or screened FP) may develop disease based on their age-specific incidence and continue to receive screening tests. People with undiagnosed disease may get screen- or clinical detection, or progress to metastatic disease before being diagnosed. The model estimates an effective test sensitivity (Sens^{eff}) that has separate components including test sensitivity (Sens), biopsy compliance (BiopComp), and biopsy detection rate (BiopDetect). The endogenous sensitivity of loco-regional, stage M0 disease is determined by the Core model presented in Essay#2. The sensitivity of distant-metastasized, stage M1 disease is assumed to be 100% accurate, as the test sensitivity increases substantially when disease has progressed beyond the loco-regional stage.

The standard for biopsy referral in the U.S. from 1990 to 2005 was a PSA level greater than 4ng/mL, yet lower thresholds were suggested and used in the 1990's, including 3 ng/ml and 2.5 ng/ml. In this model men are eligible for biopsy after screening if their PSA exceeds the endogenous threshold determined by the Core model (see Essay#2).

Screen detection rate (sx) of disease is given by age and grade. T^{sx} represents the average time between two consecutive screening tests; a testing interval of 2 years is found to be reasonably consistent with observed incidence (Gulati et al., 2010). S^s is the on-off switch for PSA screening:

$$sxM0_{i,j} = \frac{UxM0_{i,j} * F_i * SensM0^{eff} * S^S}{T^{sx}} \tag{4}$$

Not all men with a positive test result submit to a follow-up biopsy. The model base biopsy compliance rate following a positive PSA test is taken as 0.5, which is lower than in Europe, where estimates range around 0.8-0.9. In the PLCO trial of the U.S., 40% of men with a PSA between 4 and 7, 53% of men with a PSA between 7 and 10, and 69% of men with a PSA greater than 10 had a follow-up biopsy (Andriole et al., 2012).

Biopsy detection rate (or biopsy accuracy) represents the ability of biopsy to detect men with existing disease. Its value has increased with the dissemination of extended biopsy schemes over time. 4-core biopsies were standard before 1990, 6-core biopsies by 1995, and 8- to 12-core biopsies were standard by the early 2000's. A 6-core biopsy is 80% accurate, 4-core biopsy accuracy is 2/3 of this amount, and extended core biopsies, which are presently used, are 100% accurate. The biopsy detection rate varied from 0.6 to 1, based on these estimates provided in previous studies (Presti et al., 2000; Haas et al., 2007; Underwood et al., 2012)

Clinical Detection:

Disease can also be clinically detected at any stage and the clinical detection hazard by grade (Cx_j) is assumed to be much higher after metastasis of disease (Gulati et al., 2010). We do not model digital rectal exam (DRE) testing explicitly, and assume that the clinical detection hazard stays constant after the PSA era. This is an important assumption that may not be correct and may lead to overestimation of the value of the PSA test, since we do not capture any possible increases in the frequency of DRE test rate. In fact, DRE detections are also likely to increase because of disease awareness, which has increased over the years (see Essay#1).

The clinical diagnosis rate (cx) for undiagnosed (Ux) loco-regional disease is given as follows:

$$cxM0 = UxM0_{i,j} * Cx_j * C_s \tag{5}$$

Treatment Sector

There is a wide range of treatment options for prostate cancer that vary according to stage and grade, as well as patient characteristics such as age and personal preference. Primary treatment options include surgery, radiation, and conservative management, which may also involve hormonal treatment (Hoffman, 2011). Age has the biggest impact on treatment choice. Radical prostatectomy is the suggested option for younger men with localized prostate cancer and a long life expectancy, while active surveillance—formerly known as "watchful waiting"—is considered to be a more reasonable approach for older men with less aggressive disease and more serious comorbidity issues (Albertsen et al., 2005; Lu-Yao et al., 2009).

More than half (52%) of men aged below 65 are initially treated with radical prostatectomy, whereas radiation therapy is the most common treatment for men aged 65-74 (38%), and active surveillance is the major treatment of choice for men 75 years and older (61%) ([ACS Facts and Figures, 2014-2015](#)). A majority of men with localized cancer were offered aggressive treatment ([Fowler et al., 2000](#)), and rates increased substantially in the 1990's ([Lu-Yao et al., 1997](#); [Mettlin, 1997](#)) before data supported the benefit of aggressively treating early-stage cancer. The first randomized trial demonstrating a benefit for radical prostatectomy compared to watchful waiting was published in 2002 ([Holmberg et al., 2002](#)), showing a relative mortality hazard reduction of 50% for men aged 65 and below. There was no survival benefit for men above 65.

The treatment sector diagram is shown in Figure 7. Accordingly, patients who are diagnosed with prostate cancer by either screen-detection (Sx patients) or clinical detection (Cx patients) are assigned to one of the three primary treatments, classified as radical prostatectomy (RP), radiation therapy (RT), and active surveillance (AS). Initial treatment choice is classified based on the most aggressive treatment patient has received within 6 months after diagnosis (time to act=0.5 years). For example, anyone who had an RP is classified under surgical treatment even if he also received other treatments. RT and AS may also include androgen deprivation, and AS includes watchful waiting, and no treatment for simplicity.

In this setting, patients may also choose to change the initial course of treatment according to some probability (pChgTx). Patient deaths due to treatment-related procedures are ignored, assuming that they will not have a big effect on population counts. These may reach considerable numbers at lower disease thresholds, however ([Welch, 2005](#).)
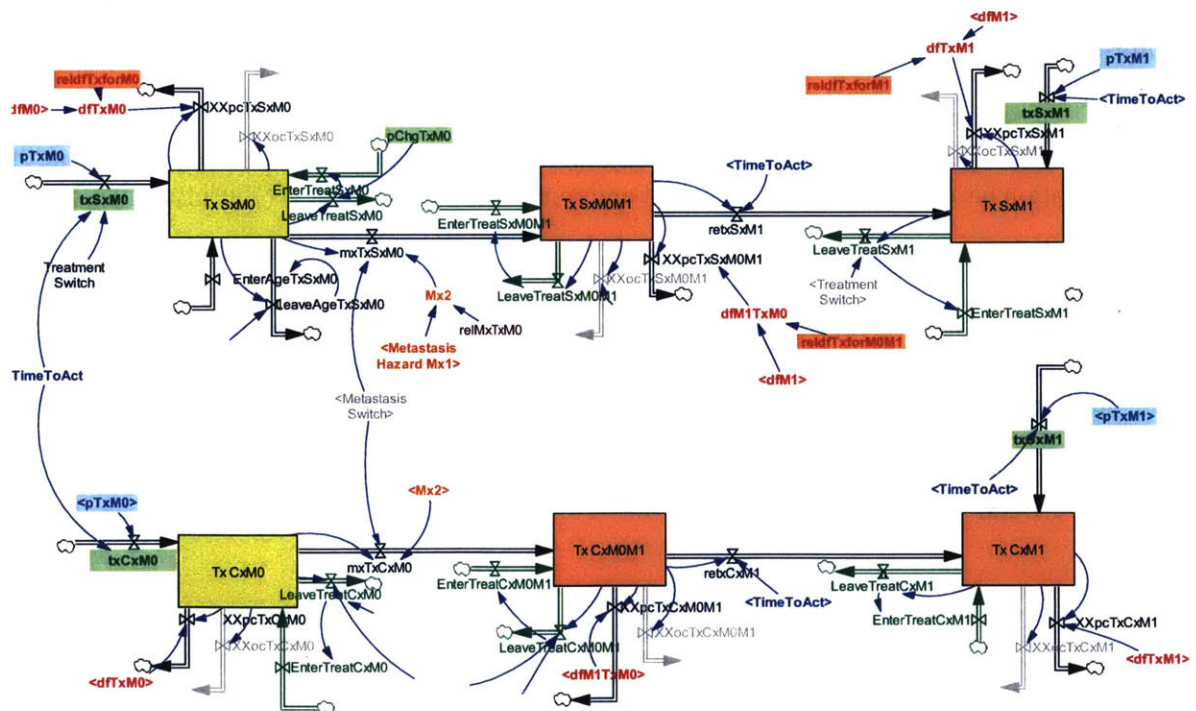
Figure 7 Treatment Sector Stock-Flow Diagram

Primary treatment choice (pTx) is exogenous to the model, based on the stage of the disease at screen or clinical detection, and treatment choice is not affected by the type of detection. Stock variables represent the treated patients (Tx), categorized by age, grade, and treatment type. The yearly treatment rate (tx) of screen-detected, stage M0 cancer is given as follows:

$$txSxM0 = \frac{SxM0_{i,j} * p^{txM0} * T_s}{\tau}$$

(6)

The treatment efficacy parameters for the three primary treatment options are chosen based on previously published studies. For RP we assume a hazard ratio of 0.56, and for RT 0.8 (Holmberg et al., 2002; Bill-Axelson et al., 2011; Hadley et al., 2010; Underwood, 2012; PSAPC Model CISNET 2009). Loco-regional disease can still metastasize after treatment, yet the metastasis rate is assumed to be slowed down after treatment. I multiplied the initial hazard of metastasis with some fraction (relMxTx) that is subscripted by treatment choice, denoting the efficacy of treatment to prevent metastasis of early-stage disease. Tx SxM0M1 and Tx CxM0M1 represent subjects who are diagnosed either by screening or clinical detection during early-stage disease and have received treatment for early-stage cancer, yet have already metastasized to distant disease.

Screening Dissemination Sector

PSA testing became widespread in the late 1980's before data supported the benefit of screening or aggressively treating diagnosed cancer (Hoffman et al., 2011). In our model, the doctor's adoption of PSA screening is modeled as a fraction that ranges between 0 and the maximum adoption fraction. Screening dissemination takes place after 1985, the year PSA screening is introduced, and rapidly diffuses in the medical community after that. The screening dissemination sector stock/flow structure is given in Figure 8.

The equation for the adoption fraction (A) is given as follows, where alpha and beta represent the dissemination parameters, estimated by first and repeat PSA screening data (Mariotto et al., 2007):

$$\frac{dA}{dt} = S_s(\alpha + \beta A(A^{max} - A))\_ifA < A^{max}, else 0$$

(7)

The current screened fraction of the population is defined as the product of the adoption fraction (A) and the screen eligible fraction (F). Screen eligibility is determined by the formal recommended starting and stopping ages in the PSA screening guidelines and the standard eligibility fraction, which indicates the maximum eligibility or the reference market for the PSA practice.

$$F = F_{std} * eff_{sa} * eff_{sa}$$

(8)
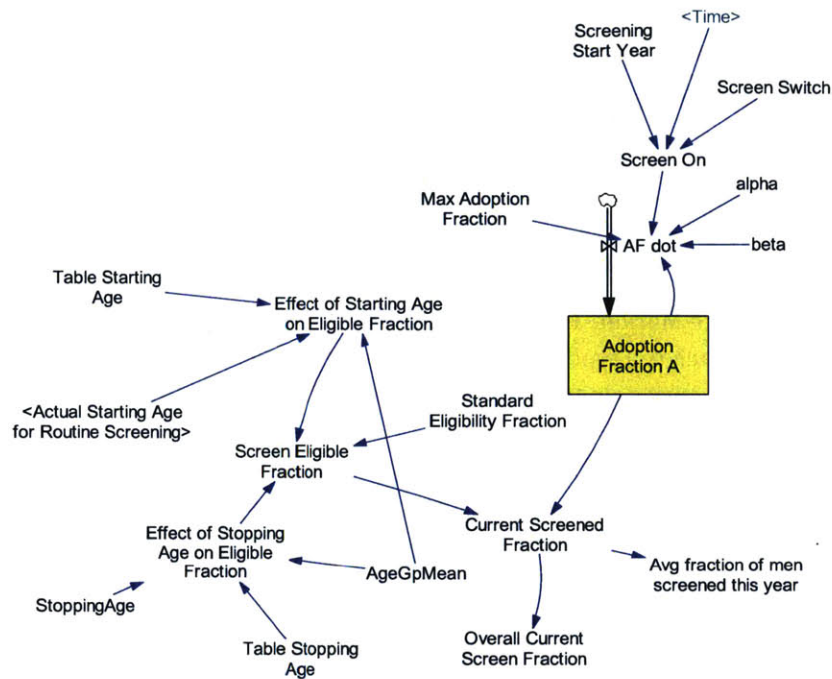
Figure 8 Screening Dissemination Sector

The effects of starting and stopping ages on the screening-eligible fraction are modeled by using graphical functions for an S-shaped curve. Accordingly, the screen-eligible fraction F is closer to maximum between the recommended ages for starting and stopping to screen; yet it fails to reach its maximum within this range, and also extends beyond the formal ranges. Both the screen-eligible fraction and the current screened fraction are given for 5-year age groups between the defined age ranges of 35-80+.

Input	Output
-10	0
-7.5	0.05
-5	0.1
-2.5	0.25
0	0.5
2.5	0.75
5	0.9
7.5	0.95
10	1
New	
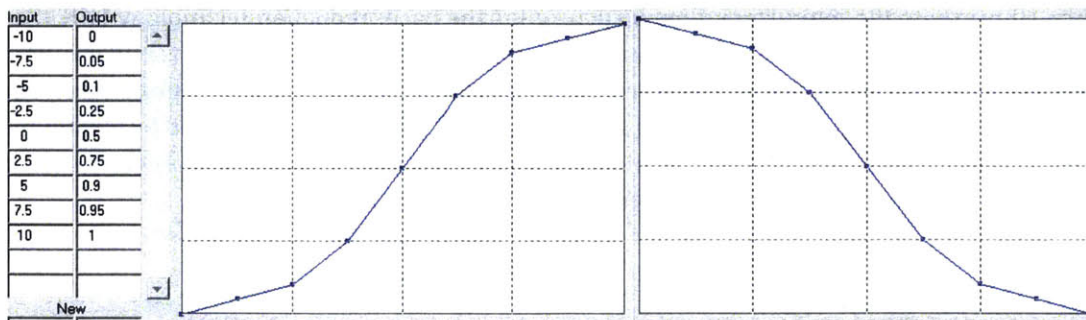
Figure 9 Tables representing the effect of starting and stopping age on screen-eligible fraction

98

Harm Reduction Technology (HRT) Sector

It is estimated that there were 3.3 million men with a history of prostate cancer living in the U.S. as of January 2016, and an additional 180,890 men will be diagnosed in 2016 (Facts and Figures 2016-2017). Many of these survivors who have been treated with surgery or radiation therapy experience incontinence, bowel complications, and/or erectile dysfunction (Resnick et al., 2013).

Radical prostatectomy has created two major medical/ industrial markets, the incontinence market, and the erectile dysfunction (ED) market:

a) The Incontinence Market: This market includes post-op procedures such as "artificial sphincters" (which is a type of implant used when patient gets incontinent after surgery), and the incontinence diaper industry, like the "Depend incontinence product line" used as a first line of treatment.

b) The Erectile Dysfunction (ED) Market: These include Viagra and similar products, used as first-line treatment following prostatectomy or the radiation therapy for prostate cancer. Second-line treatment is usually penile injections, and the last resort on this ED market pyramid is a surgical procedure known as the penile implant.

"In the case of prostate cancer you do a PSA test, leads to a biopsy, leads to treatment, leads to follow-up. If you're impotent then you want to try Viagra, Cialis, Levitra, all sorts of erectile drugs, to correct that. If you're incontinent and you can't control your flow of urine, then you have an artificial sphincter and all sorts of things. So the amount of money that you can make from an inexpensive PSA test down the road, I think far exceeds what you can make with a colonoscopy." — Richard Ablin, University of Arizona, College of Medicine, Professor of Pathology

The prostate cancer industry is a quite big market, where each pill used for ED costs $15 to $22, a prostate biopsy costs about $2000, a radical prostatectomy takes about $30,000, and about $500 million of penile implants are sold in the U.S. and $1.7 billion worldwide each year (Bloomberg News, 2013).

Figure 10 presents the main stock-flow structure for the harm reduction technology (HRT) sector built for this study. The HRT sector narrates an economic story in which the firms engaged in harm reduction look at the return to their research and development (R&D) expenditure. In this framework, the level of the HRT is defined as the fraction of the population harmed by treatment that can be treated effectively with HR technology, where T=0 means there is no HRT or treatment available, and T=1 means everyone can benefit from the available technology[4].

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[4] Please note that in this formulation the harm reduction technology (HRT) reaches its maximum value of 1 very early, and as HRT reaches its maximum level its effect on treatment harms reaches a lower bound. An alternative and better conceptualization would be to allow HRT to continue to improve over time, until its effects on treatment harms become zero.
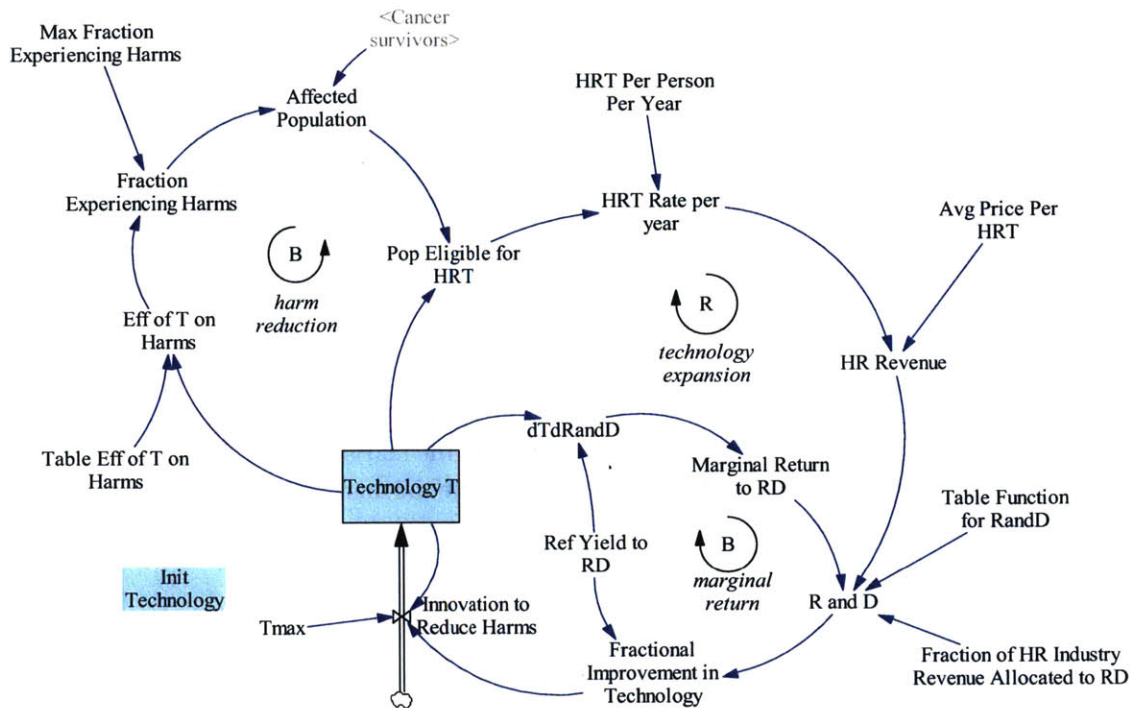
Figure 10 Harm Reduction Technology (HRT) Sector

As the HRT for prostate cancer improves, the remaining improvement declines, and with it the expected return to a dollar of new R&D. As the expected return to investment goes down, R&D will fall, causing the HRT to saturate below its theoretical maximum level (T^{max}). The rate of change in T (innovation to reduce harms) is modeled with a logistic function where γ represents the fractional improvement in technology:

$$\frac{dT}{dt} = T(T^{max} - T) * \gamma \tag{9}$$

The revenue of the HR industry equals the product of the average price of each harm reduction treatment and the treatment rate per year. Harm reduction treatment rate is defined as the population eligible for harm reduction treatment multiplied by the harm reduction treatments per person per year. Average price per HRT, and the number of HR treatments per person per year are exogenous constants.

The eligible population for HRT is defined as the product of affected population and the T, where the affected population represents the number of people who experience the side effects of treatment for prostate cancer, including urinary incontinence, bowel problems, and erectile dysfunction. The fraction experiencing harms is equal to the maximum fraction experiencing harms multiplied by the effect of HRT on harms, which is a decreasing function of T. Figure 11 gives the table of the effect of T on harms:
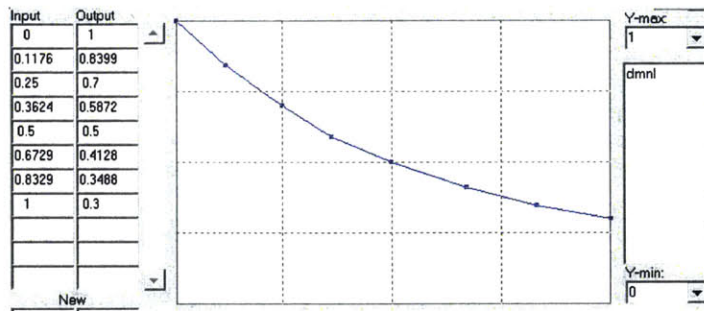
Figure 11 Table of Effect of Technology on Harms

Research and development (R&D) is defined as a fraction of the HR industry revenue, which itself is a function of expected profit per dollar of R&D. I estimate this by looking at the marginal revenue from an increase in HR Technology (T) and comparing it to the marginal cost. The fraction of the HR industry revenue allocated to R&D falls with the reduction in the marginal return to R&D. I take it as linear since no data is available on this relationship.

PSA Screening Harms and Benefits

The PSA screening harms and benefits sector calculates the perceived utilities associated with possible disease state and test outcomes for professional and advocacy groups. These utilities then determine the perceived HBR for the threshold T and the recommended starting age R after a delay that represents the time delays for assessing and diffusing the evidence and for translation of scientific evidence into policy making.

Obvious benefits of screening are a potential reduction in disease-related mortality – a benefit that some but not all randomized clinical trials have shown – and hence an increase in the number of life-years gained, and a reduction in the rate of advanced disease. Harms of screening include false positives which may cause anxiety and lead to unnecessary biopsies, and biopsies in turn have potential harms. The biggest harms of screening, however, are over-diagnosis and overtreatment, which are also the least understood harms (USPSTF, 2012; Peres, 2013). In a review paper, Croswell et al. (2011) concluded that "PSA screening for prostate cancer confers a modest mortality advantage, but at the cost of an important degree of over-diagnosis and overtreatment in the population".

Literature provides a range of utility values regarding prostate cancer health states (Bremner et al., 2007; Litwin et al., 1995). In the utility calculation module, I use the disutility parameters for having a biopsy following a false positive test, living with side effects of cancer treatment, and the disutility of end of life in terms of Quality Adjusted Life Years (QALY's).

Instantaneous biopsy disutility (ϵ) represents the one-time utility decrement associated with prostate biopsy, and varied between 0.01-0.1. The decrement of living in the treatment state (φ) was varied using 0.05 and 0.24 from Bremner et al. (2007). The utilities for living with treatment before or after metastasis are associated with different disutility values; we combine them into one parameter. The disutility associated with death, or the end of life disutility (ρ), is varied from 0.5-1. We assume the morbidity from the disease itself is zero. The parameters used are listed in Table 2.

101

These disutility values are used to build a baseline disutility matrix for three possible disease states of D+ (progressive disease), D⁰ (indolent disease), and D- (healthy); and the two possible test outcomes associated with these: T+ (test positive) and T- (test negative), using the disutility values above. This matrix shown in Table 2 forms the basis of the evidence-based harm and benefits calculation.

Table 6 Baseline disutility matrix for professional and evidence-based groups

	D- (HEALTHY)	D⁰ (INDOLENT)	D+ (DISEASED)
T+	disutility(D-T+)	disutility(D⁰T+)	disutility(D+T+)
T-	disutility(D-T-)	disutility(D⁰T-)	disutility(D+T-)

The disutility associated with a false positive test followed by a biopsy is the potential biopsy disutility. The probability of the follow-up after a positive test result is given with the parameter biopsy compliance (BiopComp). The disutility associated with an indolent tumor is equal to the treatment disutility, and the disutility associated with a true positive tumor is equal to the treatment disutility plus the potential death of the patient, which is assumed to be lower with screening (PrPCaDeathWithSx).

We assume the disutility for a negative test for a healthy patient, and for a patient with an indolent tumor, to be zero. The disutility associated with a false negative test result for a relevant cancer case is the biggest one of all six cells. It is equal to the disutility associated with end of life (EOL) of the patient, should they die from cancer, which we assume is higher without screening. The equations for non-negative disutilities are given below:

$$\text{Disutility (D-T+)} = \text{Biopsy Disutility} * \quad \text{BiopComp} \tag{10}$$

$$\text{Disutility (D⁰T+)} = \text{Disutility Due to Treatm} \tag{11}$$

$$\text{Disutility (D+T+)} = \text{Disutility Due to Treatm} + \text{Disutility EOL} * \text{PrPCaDeathWithSx} \tag{12}$$

$$\text{Disutility (D+T-)} = \text{Disutility EOL} * \text{PrCaDeathWithoutSx} \tag{13}$$

The baseline matrix represents the disutility values before the harm reduction technology (HRT) decreases the harms associated with treatment. Over the years, the HRT has decreased the side effects of prostate cancer treatment and also the disutility associated with the biopsy.

The effect of the HRT on harms is found by normalizing the effect of current level of technology on harms to its initial level. Then the treatment disutilities from the base matrix are multiplied with the effect of HRT on treatment harms and the false negative cases that do not receive treatment.

This modified baseline disutility matrix represents the professionals, or evidence-based groups' perceptions on benefits and harms for each possible test outcome and disease state combination. Here the main assumption is that evidence-based groups are acknowledging the possibility of over-diagnosis, and taking it into account in their harms and benefits calculations, along with the false positives.

Most patient advocacy groups, patients themselves, and laypeople, on the other hand, are usually not aware of the possibility of indolent disease, and the fact that some disease may not cause any harms

if not detected and left untreated. There is some degree of awareness about the possibility of false positives, however.

These propositions and assumptions are in line with the data collection from the expert interviews and medical literature. I found that the opinions of professionals and patients/advocacy groups diverge substantially when it comes to perceived harms and benefits of screening:

"The most important harms [of screening] are really over-diagnosis and over-treatment. Those are basically the most important ones. To get a good schedule on that is crucial." — *Harry de Koning, Professor of Evaluation of Screening, Biochemistry and Pharmacology, CISNET*

"The potential benefit is finding a cancer that may harm the patient within his remaining lifetime. The disadvantage is what we call 'PSA anxiety,' in other words, concern on the part of the patient about having an undetected cancer in spite of a normal finding. The others are the risks of biopsy, which are sepsis, urinary tract infection without sepsis, bleeding, urinary retention... Interviewer: Are these common after biopsy or are they considered to be rare cases? JB: They're unusual, I would say probably the nature of 4%, maybe 5%." — *John D. Barry, Professor of Urology and a Professor of Surgery, Oregon Health and Science University, former chair of American Urological Association*

"I hear a lot said about false positives and that they don't want to screen women because of false positives, and that for every, I think, 1900 women screened there will be 5 that are identified, one of which will ultimately be a breast cancer and 4 of which will either get additional screening or biopsy, some people would say unnecessarily. But all the women that I speak to, and I say that to, say they would much rather go through a little anxiety, because that's the big excuse given, I think, that 'We don't want to cause these women undue anxiety.' But I think women will tell you that they'd rather go through a little bit of anxiety and a biopsy or additional pictures, through mammogram or ultrasound or MRI, than go undetected. Because mortality's higher at late stage, and that's a fact." — *Patient Advocate*

"So I don't think women are wrong or uninformed for wanting to have mammograms. Each woman must navigate the benefits and harms of screening for herself, in a way that attends to her overall wellbeing. Which is situated within the culture that we live in, including fear of death and fear of breast cancer. Some women are terrified of breast cancer and for some of these women the risk of overdiagnosis, overtreatment, false positive, etcetera, those are pale in comparison to their fear." — *Karuna Jaggar, Executive Director, Breast Cancer Action*

This major difference in perceptions between the professionals and the advocacy and patient groups is represented by a modification of the evidence-based matrix for the laypersons, which reduces the three-by-two disutility matrix to a two-by-two matrix, where there are only diseased and healthy states, and no indolent state (Table 3). Note that both professionals and laypeople/advocates consider the effect of the HRT on harm reduction.

Table 7 Baseline disutility matrix for patient advocacy groups, patients and laypeople

	D- (HEALTHY)	D+ (DISEASED)
T+	disutility(D-T+)	disutility(D+T+)
T-	disutility(D-T-)	disutility(D+T-)

Our ultimate objective is to calculate the perceived change in the total disutility for a small change in the biopsy threshold (delta), so that marginal harms benefit ratio can be approximated. Objectively,

this marginal harms or benefits number should determine the value in expanding or narrowing the scope of screening. A bigger than one marginal harms to benefit ratio signals the disutility of the test for marginal people being tested at the threshold, and thus warrants an expansion of threshold (i.e. limiting the test to people with higher PSA levels). A marginal value below one gives the opposite signal. In order to obtain this value the disutility values associated with each possible disease state/test outcome option are multiplied by the rate of change (due to the small change in threshold) in prevalence for each of the six (or four) states. For professionals, this incremental change is represented with variables F1-F6; equations are given in Table 4. The variable Prev indicates the endogenous disease prevalence coming from the model including D^+ and D^0 subjects, and the variable Fracindolent indicates the fraction of D^0 to D^+.

Advocacy groups, on the other hand, do not distinguish between D^0 and D^+ states, and their degree of understanding of false positives and over-diagnosis also varies as a weight parameter changes between 0 and 1 (Table 5). As weight becomes equal to zero, a layperson (over-simply) assumes that D+ is equal to T^+, and D- is equal to T^-, i.e., that everyone who gets a positive test result has the disease and everyone with a negative test result is healthy.

Table 8 Table for Perceived Incremental Change (F11-F44) in prevalence for professionals

	D- (HEALTHY)	D⁰ (INDOLENT)	D+ (DISEASED)
T+	F1 = dFP*(1-Prev)	F2 = dTP*Prev*(Fracindolent)	F3 = dTP*Prev*(1-Fracindolent)
T-	F4 = -dFP*(1-Prev)	F5 = -dTP*Prev*(Fracindolent)	F6 = -dTP*Prev*(1-Fracindolent)

Table 9 Table for Perceived Incremental change (F11-F44) in prevalence for advocacy groups

	D- (HEALTHY)	D+ (DISEASED)
T+	F11=F1*weight	F22=(F2+F3)*weight+PDplus*(1-weight)
T-	F33=F4*weight+PDminus*(1-weight)	F44=(F5+F6)*weight

The variables dFP and dTP represent the incremental change in the false and the true positive fractions as the biopsy threshold T moves in one direction. Note that there is a tradeoff between true and false positives, and true and false negatives. As one moves in a direction, the other one also moves in the same direction (Figure 12 and Table 4).
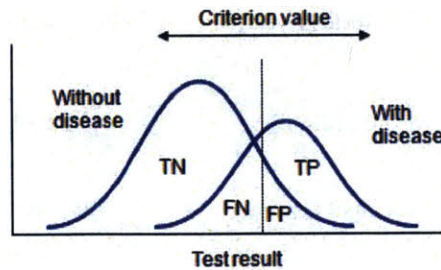
Figure 28 Distributions of 2 hypothetical D+ (diseased) and D-(healthy) populations with respect to a certain threshold

Ultimately, the weighted disutilities for professionals and advocates are calculated by multiplying the utility matrix elements with the perceived incremental change, to come up with the weighted disutility values for an incremental change in threshold T. "EB" represents "evidence-based."

Weighted Disutility EB= F1*UtilityDminusTplus+ F2*UtilityDzeroTplus+
F3*UtilityDplusTplus+ F4*UtilityDminusTminus+ F5*UtilityDzeroTminus+ F6*UtilityDplusTminus
(14)

Weighted Disutility Layperson= F11*UtilityDminusTplus+ F22*UtilityDplusTplus+
F33*UtilityDminusTminus+ F44*UtilityDplusTminus
(15)

These weighted disutilities are then used to calculate a "Pseudo HBR" that is used as a signal to find the HBR for the threshold. This signal has two components, one for professionals and one for advocates. The signal enters a simple filter that amplifies its effect:

Pseudo HBR [prof] = 1-Weighted Disutility EB*Sensitivity of HBR to Utility
(16)

Pseudo HBR [advoc] = 1-Weighted Disutility layperson*Sensitivity of HBR to Utility
(17)

HBR for Action = IF THEN ELSE(Pseudo HBR[group]>1,Max(HBRMinSignal+1,Pseudo
HBR[group]),Min(1-HBRMinSignal,Pseudo HBR[group]))
(18)

We also assume that there is a delay between the HBR for Action and the Perceived HBR, which represents the translation delay of scientific evidence into policy making:

Perceived HBR= SMOOTH3 (IF THEN ELSE (Time<Guideline Start Year [group],
1+InitialHBRBias [group], HBR for Action [group]), HBR Trans Delay)
(19)

Parameter Overview

Table 6 lists important model inputs and symbols used throughout the paper with the range used for sensitivity analysis, and associated data sources. Figure 12 shows a table for key outcome measures for the prostate cancer model, categorized as incidence variables, prevalence variables, and cumulative totals of these throughout the simulation horizon.

Table 10 List of Important Model Inputs

Name	Parameter [unit]	Range	Source(s)
Prostate cancer specific mortality fraction (by grade)	dfM0, dfM1 [1/year]	[0.07-0.37]	SEER survival curves by stage, Messing et al., 2006; Aus et al., 2005; Etzioni et al., 1999
All-cause death fraction (by age group)	dfAll$_t$ [1/year]	Age specific	Sex and age-specific Census and Vital Stats. Life tables for the US Social Security Area 1900-2100.
Probability of indolent tumor at onset	pOx [dmnl]	[0.2-0.6]	Expert judgement
Hazard of transition to metastatic disease (by grade)	Mx1, Mx2 [1/year]	[0-0.05]	Ghani et al., 2005; Scardino et al., 1994; Underwood, 2012; Gulati et al., 2010
Pre-metastasis clinical diagnosis hazard (by age, grade)	Cx1, Cx2 [1/year]	[0-0.03]	Gulati et al., 2010; Etzioni et al., 1999
Multiplier for Hazard of Clinical Diagnosis (by age)	MCx [dmnl]	[15-25]	Gulati et al., 2010

105

Hazard asymptomatic onset (by age)	0x [1/year]	Age specific	Cowen et al., 1994; Etzioni et al., 1999; Bubendorf et al., 2000; Underwood, et al., 2012
Time between screenings	TimeBtwSx [year]	[2]	Gulati et al., 2010
Biopsy compliance (by stage)	BiopCompM0 [dmnl]	[0.3-0.7]	Andriole et al., 2009; Gulati et al., 2010
Prostate biopsy detection rate (by stage, calendar year)	BiopDetectM0 [dmnl]	[0.64-1.0]	Haas et al., 2007;
Probability of treatment (by treatment type)	pTxM0 [dmnl]	[0.1-0.5	ACS Facts and Figures, 2014-2015
Relative death fraction (by treatment)	reldfTxforM0 [dmnl]	[0.1-1.0]	Holmberg et al., 2002; Bill-Axelson et al., 2011
Time to act	τ [year]	0.5	Hoffman et al., 2003
alpha	α [1/year]	[0.015-0.03]	Based on PSA test dissemination curve by Mariotto et al. (2007)
beta	β [1/year]	[0.45-0.65]	Based on PSA test dissemination curve by Mariotto et al. (2007)
Maximum adoption fraction	A^{max} [dmnl]	0.7-0.9	Expert judgement
Stopping age to screen	Age^{stop} [years]	75-85	Expert judgement
Annual utility decrement of living with treatment	φ [dmnl]	[0.05-0.24]	Bremner et al., 2007
Utility decrement of End of Life	ρ [dmnl]	[0.15-0.46]	Krahn et al., 2003; Sandblom et al., 2004
Biopsy utility decrement	ϵ [dmnl]	[0.01-0.1]	Underwood et al., 2012
HBR Translation Delay	τ [year]	2-6	Expert judgement

Key Outcome Measures

Performance metrics of the model can be categorized under three groups: incidence variables, which are the important rates of changes in the simulation; prevalence variables, which show the current levels of the critical metrics; and the total cumulatives, which keep track of the cumulative values of some important measures, such as cumulative number of tests, or diagnosed cases since the beginning of the simulation. Table 7 tabulates a list of important outcome measures of the model.

The following key performance indicators are used to assess the policy outcomes in the analysis: The age to start routine screening, the biopsy threshold, perceived HBR, number of survivors, and percent of overdiagnosed cases. The reasons for choosing these key outcome measures are to i) keep track of

the most critical stocks for the cancer screening problem, to ii) provide insights into different features of the system, to iii) inform policy makers regarding the tradeoffs of each indicator and to iv) apply the notion of multiplism suggesting that a problem should be measured in different ways (Dunn, 2016).

The age to start routine screening and the biopsy threshold are the most important breadth indications for cancer screening, and their formal recommended values are readily available in the literature. However, the actual values used in practice are unknown, or only traces of information are available, as they are hard to observe and measure. In spite of their importance, modeling studies rarely consider these metrics. Cancer survivors are of particular concern in the U.S., as their numbers are growing and adding more pressure to the healthcare system (DeSantis et al., 2014). Overdiagnosis is another contentious issue with important implications for policy-making. Models of cancer registry data and trial results estimate that 23% to 42% of PSA-detected cancers would not be found without screening (Hoffman and Zeliadt, 2010), and 42-66% of all diagnosed prostate cancers would have caused no clinical harm had they remained undetected (Draisma et al., 2009).

Table 11 Outcome measures of the model categorized by type

	INCIDENCE VARIABLES		PREVALENCE VARIABLES			CUMULATIVES
Prostate Cancer (PCa) ☹	Real PCa Incidence <Real PCa Incidence, by age>	Estimated Incidence <Reported PCa Incidence>	Real PCa Prevalence (people) <Fract of Real PCa Prevalence>	Estimated Prevalence <Fract of Reported Prevalence or ever diagnosed>	<Fract Reported PCa Prevalence by age> <Reported PCa Prevalence by age>	Cum Nr PCa <Cum Nr PCa Cases Diagnosed>
Screening ⩗	Screening Rate <PSA Screening Rate>	<First PSA Screening Rate> <Repeat PSA Screening Rate>	Screening Prevalence <Nr Men Ever Had PSA>	<Fract of Popn Ever Screened>	% M0-M1 <Fract M0 at Detection>	Cum Nr PSA Tests <Cum Nr PSA Tests>
Biopsies 😖	Biopsy Rate <Biopsy Rate by age>	<Unnecessary Biopsy Rate by age>	% Healthy with FP <Fract of Healthy Popn Living with FP>	% Ever Had Biopsy <Fract Ever Had Biopsy>	<Fract of PSA Detected>	Cum Nr Biopsies <Cum Nr of Unnecessary Biopsies>
Treatment	Treatment Rate (people/yr) <txRate by treatment>	Screen Detected Treatment Rate <txRateSx>	<Fract Ever Diagnosed by age>	<Treated Total> <Nr Treated by age> <Nr Treated by grade>	<Fract Treated>	Cum Total Treatments <CumTotal TxPCa>
Cost of Care ⌴	Current Cost ($/yr) Treat Cost ($/yr) <Current Cost by grade> <Cost of Treatment by grade>	% Cost End of Life <Fract of Cost EOL by grade>	N/A	N/A	N/A	Cum Cost Treatment Cum Cost ($ to date) <Cum Cost Treatment>
Quality of Life ⚖	Disutility Rate Per Year <duRateTotal by grade>	Disutility Rate Biopsy <duRateBiopsy>	N/A	N/A	N/A	Cum QALY Cum Disutility <Cum Disutility>
Mortality ⌢	Real PCa Death Rate (people/yr) <XXpcbyAge> <PCa Deaths as a Fraction of Total Deaths>	Estimated PCa Death Rate <XXpcEstimatedTotal>	N/A	N/A	N/A	Cum PCa Deaths <Cum Total PCa Deaths of Men with PCa>

Validation and Analysis of the PSA Model

Experiments with model, extreme condition testing

The objective of the validation section is to demonstrate and analyze the results of the simulations conducted in order to test the validity of the model described in the previous chapter, with respect to the purpose of the model. The model is simulated via Vensim software and the simulation time

unit is years. A sufficiently small time step (1/8) is used for the simulation. The time horizon is selected as 1980-2040, about 60 years, in order to capture the dynamic trends in the diffusion of screening and compliance with recommendations, and the potential trajectories for selected policy variables. Since some of the system behavior is evident only in the long run, the time horizon of the model is set as high as 60 years, when necessary.

First, we tested the model response to a series of extreme conditions to check its robustness. An example is given in Figure 13, which shows the fraction of loco-regional, M0 disease at detection, and by grade. As expected, indolent disease cannot get detected in the absence of PSA screening, and after screening gets introduced, indolent disease at detection becomes 100%, as indolent disease cannot get metastasized by definition.
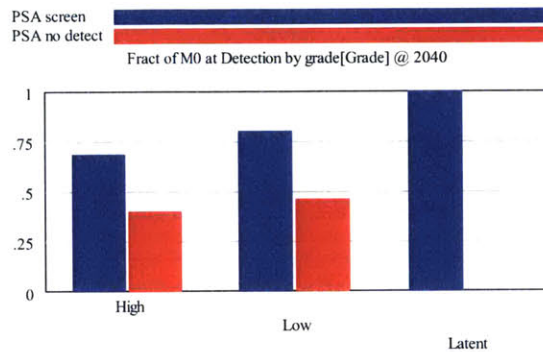
Figure 29 Fraction of loco-regional disease at detection, by grade

Table 8 summarizes the qualitative behavior of the model under selected extreme conditions and some logic tests. It can be seen that the model behavior matches the behavior expected from the model for the listed conditions, and passes the logic tests. Throughout the model-building process we also tested the model's mass balance for the population counts by calculating the sum of all the stocks in the model and comparing it against the integration of the net inflow over the simulation horizon. The only inflow to the population stocks is the male-population-turning-35 exogenous time series, and the net immigration flows. The outflow is comprised of prostate cancer deaths, and all-other-cause deaths.

Table 12 Table of extreme condition tests with the corresponding qualitative behavior

Extreme Condition Test	Qualitative Behavior
Screening switch turned off	PSA screening tests go to zero, % Ever had PSA goes to zero, % of Screen detected cancer goes to zero, % of Clinically detected cancer goes to %100, Reported PCa prevalence goes down, % of men healthy with a FP goes to zero, no detection, and treatment of latent (indolent) disease
Clinical detection switch turned off	% of Cancer clinically detected goes to zero, All cancer detection is through PSA screening
Both screen and clinical detection switches turned off	Reported PCa incidence goes to zero, Reported PCa prevalence goes to zero, no new PCa cancer survivors

Treatment switch turned off	% Ever treated goes to zero, There are no survivors with primary treatment
Treatment is 100% effective	No one dies of prostate cancer, M0 and M1 PCa deaths go to zero
Metastasis switch turned off	M0 loco-regional disease doesn't get metastasized, no distant M1 cases, no M1 prostate cancer deaths
All-cause mortality turned off	Mean population age increases, only deaths are PCa deaths
Decrease in mortality trend is removed	Overall deaths increase, population's mean age goes down
All disease is indolent	No prostate cancer deaths, 100% overdiagnosis
Other logic tests	
% PSA detected	% of disease detected by screening is 100% for indolent disease (Latent cancer cannot get detected clinically)
PCa incidence/prevalence	Reported PCa incidence is higher for older age groups
% Loco-regional at detection	100% for latent disease, as latent disease cannot get metastasized to M1 disease
% Distant at detection	0% for latent disease, higher for higher grade cancer

Basic dynamics of the model

In this section the basic dynamics of the simulation model are outlined. I will first show correspondence to historical data on various metrics including population counts, death rates, and some metrics on disease progression. Then policy-relevant factors and analysis in the base run will be shown, which replicates history and shows the future trajectory. Finally, policy tests will be conducted that change relevant policy factors and show the key results. 1980-2015 is the period for which historical data is available, and 2015-2040 is the period for possible future trajectories and implications.

Historical Data

Figures 11 and 13 give the correspondence of the model to historical data and future projections for the population stocks, including the total population, percent of population above 65 years old, and for various age groups. It should be noted that the mean age of the population decreases first until the end of the 1990's, and then it starts to increase with a decreasing rate till the end of the simulation time horizon.

Aging of the population and increase in life expectancy has serious implications for chronic disease incidence and prevalence. Prostate cancer is an age-related disease and aging of the male population implies more prostate cancer survivors in the future, especially if the current trends of screening continue at the current pace.

Pop Total

People

- Total Popn : PSA screen
- Total Popn Time Series 1979to2014 : PSA screen
- Adult men popn count TOTAL projection millions : PS

Percent Over 65

Dmnl

- Percent Over 65 : PSA screen
- Percent Over 65 DATA : PSA screen

Mean Age

dmnl

- Mean Age Simulation : PSA screen2
- Mean Age Data1980to2014 : PSA screen2
- Mean Age Data : PSA screen2
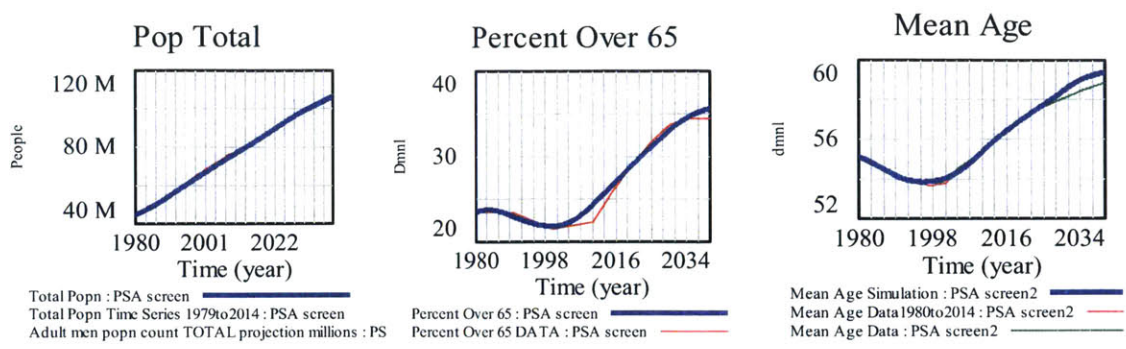
Figure 30 Total population and percent of men over 65 years and older

Population Structure 65+ vs 65-

People

- Total Popn below 65 : PSA screen
- Total Popn above 65 : PSA screen
- Adult men popn count 65minus data : PSA screen
- Adult men popn count 65plus data : PSA screen

Population Structure 50+ vs 50-

People

- Total Popn below 50 : PSA screen
- Total Popn above 50 : PSA screen
- Adult men popn count 50minus data : PSA screen
- Adult men popn count 50plus data : PSA screen

Pop 30s and 40s

People

- Popn 35to39 : PSA screen
- Popn 40to49 : PSA screen
- Popn 35to39 Data
- Popn 40to49 Data

Pop 50s and 60s

People

- Popn 50to59 : PSA screen
- Popn 60to69 : PSA screen
- Popn 50to59 Data
- Popn 60to69 Data

Pop 70s and 80+

People

- Popn 70to79 : PSA screen
- Popn 80plus : PSA screen
- Popn 70to79 Data
- Popn 80+ Data

Pop 35 to 44

People

- Popn 35to44 : PSA screen
- Pop Time Series 35to44 : PSA screen
- Adult men popn counts 35to44 : PSA screen

Pop 45 to 54

People

- Popn 45to54 : PSA screen
- Pop Time Series 45to54 : PSA screen
- Adult men popn counts 45to54 : PSA screen

Pop 55 to 64

People

- Popn 55to64 : PSA screen
- Pop Time Series 55to64 : PSA screen
- Adult men popn counts 55to64 : PSA screen

110

Pop 65 to 74

Pop 75 plus

Popn 65to74 : PSA screen
Pop Time Series 65to74 : PSA screen
Adult men popn counts 65to74 : PSA screen

Popn 75plus : PSA screen
Pop Time Series 75plus : PSA screen
Adult men popn counts 75plus : PSA screen

Figure 31 Population counts history and projection for various age groups

The death rate is given both in terms of millions of deaths per year, and also as a crude death rate, expressed as the number of deaths reported each calendar year per factor selected. The default factor at the CDC compressed mortality file is per 100,000 population, reporting the death rate per 100,000 persons. Rates are also given for three age groups, 35-55-year-olds, 55-75-year-olds, and 75+ year-olds. Model behavior shows reasonable correspondence to historical behavior of the total population counts and deaths.

Death Rate

Crude Death Rate

XXTotalAllAges : PSA screen
XXTotalAllAgesDATA : PSA screen

Crude Death Rate All Ages : PSA screen
Crude Death Rate All Ages DATA : PSA screen

111

Crude Death Rate 35-55

People/year

800 — 400 — 0

1980   2001   2022
Time (year)

Crude Rate 35to44 : PSA screen
Crude RateTime Series 35to44 : PSA screen
Crude Rate 45to54 : PSA screen
Crude RateTime Series 45to54 : PSA screen

Crude Death Rate 55-75

People/year

5000 — 2500 — 0

1980   2001   2022
Time (year)

Crude Rate 55to64 : PSA screen
Crude RateTime Series 55to64 : PSA screen
Crude Rate 65to74 : PSA screen
Crude RateTime Series 65to74 : PSA screen

Crude Death Rate 75plus

People/year

14,000 — 10,000 — 6000

1980   2004   2028
Time (year)

Crude Rate 75plus : PSA screen
Crude RateTime Series 75plus : PSA screen

Death Rate 35-55

People/year

150,000 — 75,000 — 0

1980   2004   2028
Time (year)

XXtotal35to44 : PSA screen
Deaths Time Series 35to44 : PSA screen
XXtotal45to54 : PSA screen
Deaths Time Series 45to54 : PSA screen

Death Rate 55-75

People/year

400,000 — 200,000 — 0

1980   2004   2028
Time (year)

XXtotal55to64 : PSA screen
Deaths Time Series 55to64 : PSA screen
XXtotal65to74 : PSA screen
Deaths Time Series 65to74 : PSA screen

Death Rate 75+

People/year

2 M — 1 M — 0

1980   2001   2022
Time (year)

XXtotal75plus : PSA screen
Deaths Time Series 75plus : PSA screen

Figure 16 shows the fraction of men with prostate cancer tumor at autopsy, which is used as a proxy for real underlying cancer prevalence. The prevalence estimates are from Carter et al. (1990), who studied 5250 autopsies from the U.S. literature. Estimates apply to the symptom-free male population; men with a prostate cancer diagnosis are excluded. It should, however, be noted that autopsy studies conducted more recently are finding a higher age-specific prevalence of disease (Bell et al., 2015; Jahn et al., 2015), so these estimates should be viewed as conservative with respect to the real underlying asymptomatic disease in men.

Prostate with Tumor (%)

■ Carter prevalence   ■ Model prevalence

45
40
35
30
25
20
15
10
5
0

20-30   30-40   40-50   50-60   60-70   70-80   80+
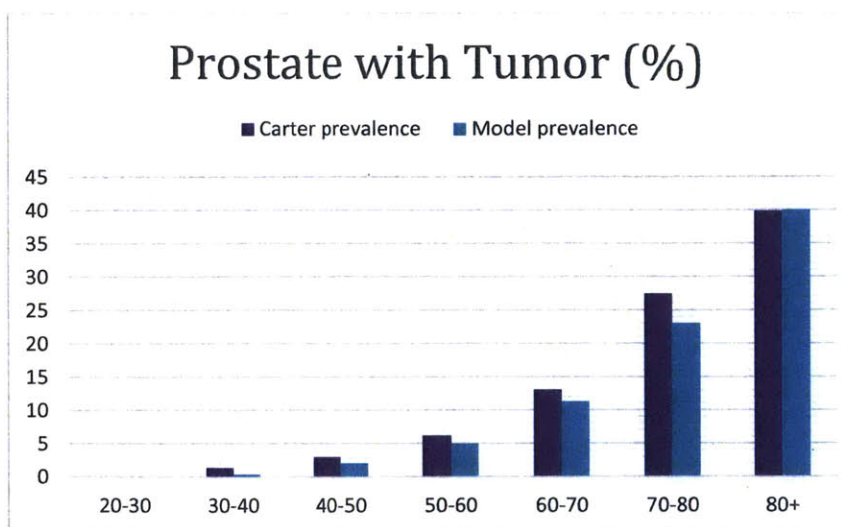
Figure 32 Age-specific prevalence of asymptomatic prostate cancer among symptom-free men based on autopsy studies published between 1941 and 1966 (Carter et al., 1990)

112

The data for the frequency of a first PSA test and of repeat tests in the United States is obtained from data generated by Wever et al. ([2010](#)) based on the approach described by Mariotto et al. ([2007](#)). The frequencies are for men aged 50–84 years. The PSA screening adoption parameters α and β are estimated based on these curves (Figure 17a), and model simulation results in the base case simulation versus data is given in Figure 17b. Time between screenings is taken as 2 years.
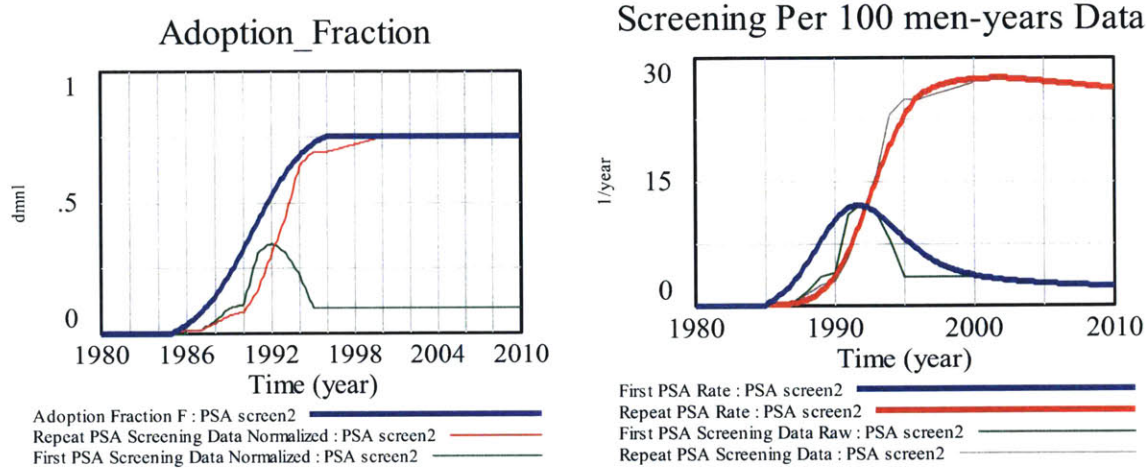
Figure 33 Frequency of first prostate-specific antigen (PSA) tests and repeat tests in the US population. Frequencies for men aged 50-84 years.

PSA screening can detect approximately 80% to 85% of prostate cancers but has a high false-positive rate, i.e., a high sensitivity yet a low specificity. The PSA test sensitivity is around 80-85%, and test specificity is 40% at 4 ng/ml with a positive predictive value (PPV) between 28-35% in asymptomatic men ([Woolf, 2001](#)). This means that, on average, 60% of all test results are false positives. The baseline simulation results given in Figure 18b replicate this feature of the PSA test. Figure 18a shows an empirical ROC curve versus model result, and the rate at which true and false positives are changing. Since each point on the ROC curve corresponds to a sensitivity-specificity pair for a certain threshold, the wide range indicates oscillations in the actual threshold. Figure 16b shows the tradeoff between test sensitivity and specificity, and suggests that specificity reached values as low as 25% in the 1990's when screening was overused, which corresponds to a false positive rate of 75%.

ROC_Curve_Model

Sens Specs

True Positive Rate ●●●●●●●●●●●●●●●●●●●●●●●●
Empirical TPR : PSA screen2 ●●●●●●●●●●●●●●●●●●●●●●

Sensitivity : PSA screen2 ——————————
Specificity : PSA screen2 ——————————
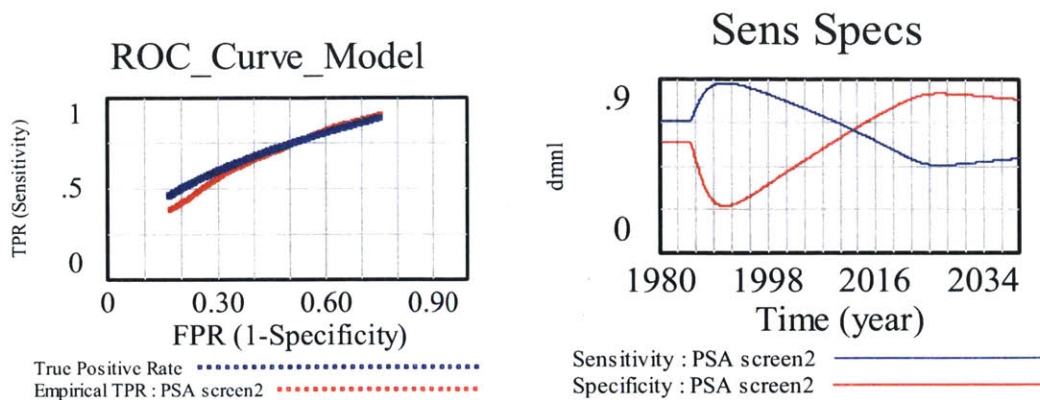
Figure 34 a) ROC curve, and b) Sensitivity and specificity of the PSA test

Figure 19 shows the data versus simulation results for proportion of the cancer stage at diagnosis. In 1980, loco-regional (M0) tumors constituted 75% of newly diagnosed and staged cases. This value is increased to 96% of all detected cases in 2002 with advances in early detection (Etzioni et al., 2008). Between 1999 and 2006, at the time of diagnosis, only 4% of tumors were metastasized (Altekruse et al., 2010).

Stage at Diagnosis

■ Stage at Diagnosis M0 Data   ■ Stage at Diagnosis M0 Simulation
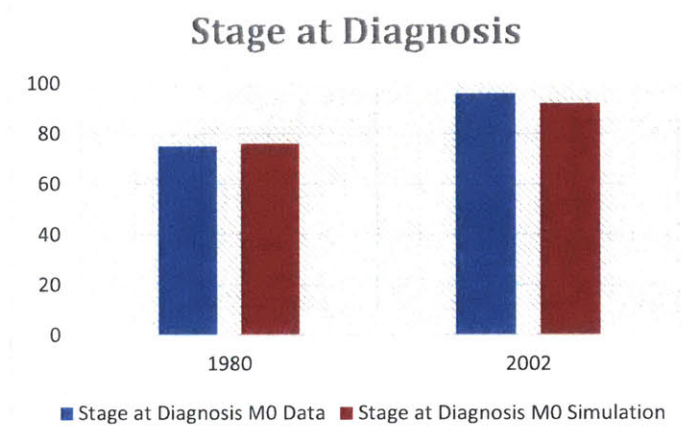
Figure 35 Stage at diagnosis

In the United States, approximately 90% of prostate cancers are detected by means of screening. The lifetime risk of receiving a diagnosis of prostate cancer nearly doubled after the introduction of PSA testing, and increased from approximately 9% in 1985 (Seidman et al., 1985) to 16% in 2007 (Altekruse et al., 2010). Figure 20 gives data versus model results for the lifetime risk of getting a diagnosis in the base case simulation.

114

Lifetime Risk of Getting a Diagnosis
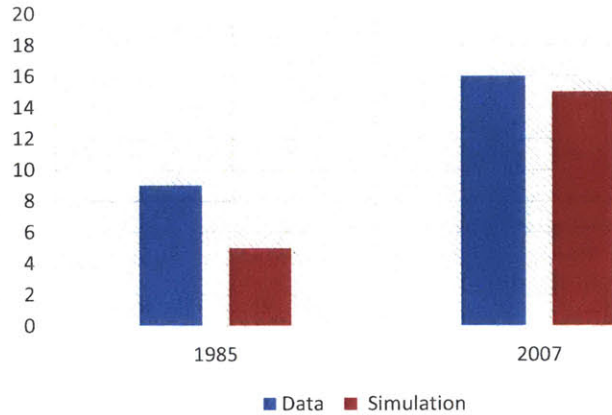
Figure 36 Lifetime risk of getting a diagnosis

Figure 21 shows the real prostate cancer incidence data from the NCI-SEER database (red line) compared to model behavior (blue line). There is an approximate correspondence between incidence data and the aggregate model output for the base case simulation. The value for the clinical diagnosis hazard before PSA screening can be further calibrated based on data.
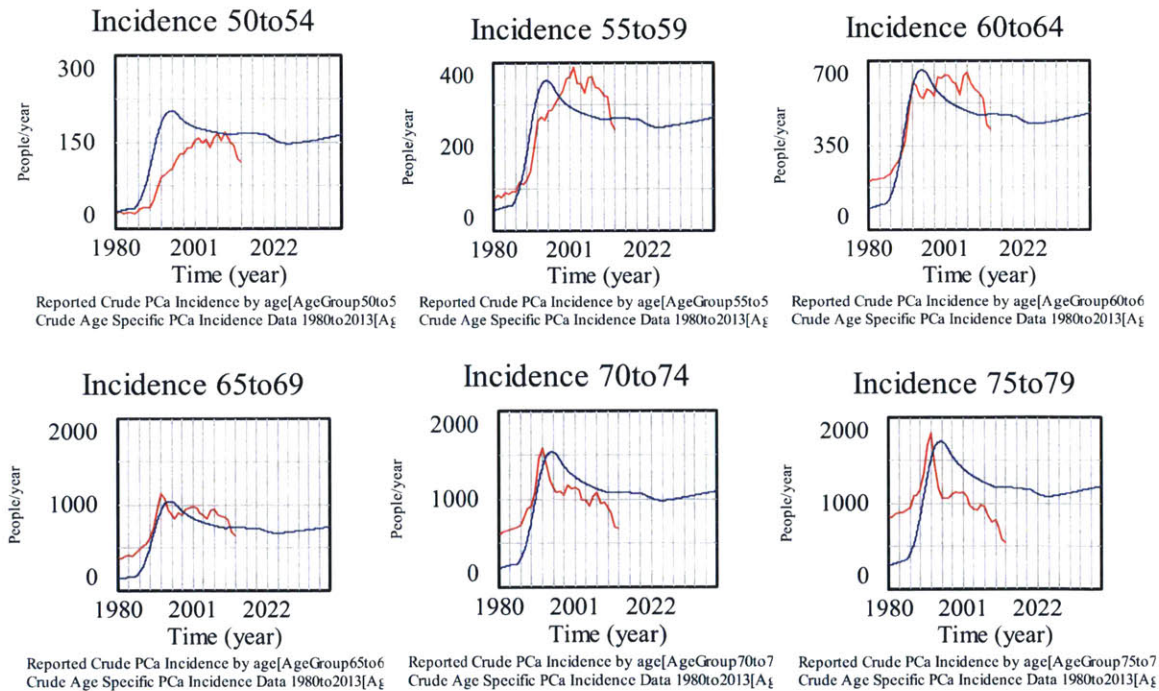
Figure 37 Prostate cancer incidence data and projection in base case simulation

115

Figure 22 gives the behavior of the harm reduction technology (HRT) in the base case run, and the rate of innovation to reduce harms. HRT follows an S-shaped curve, and innovation to reduce harms peaks in the late 1990's.
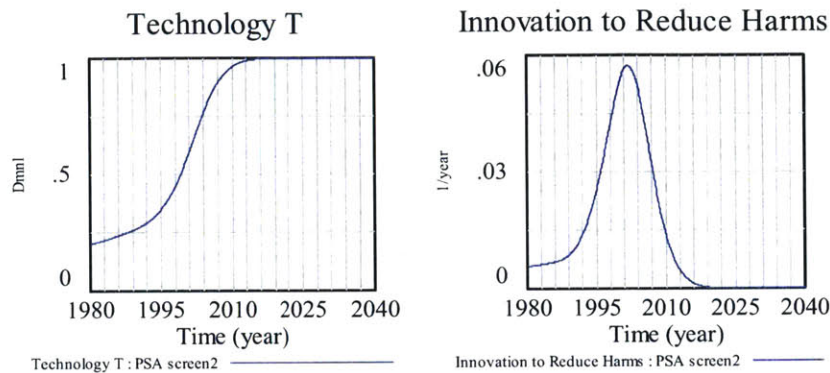
Figure 38 Reference behavior of harm reduction technology and innovation to reduce harms

Other interesting variables for which we were not able to find historical data are the fraction of the healthy male population currently living with a false positive, and the fraction of diseased in the target screening population. These metrics are potentially very important ones, yet not readily measured or considered in existing medical papers and modeling studies. Simulation results show that the fraction of false positives in the healthy male population may have increased to as high as 18% in the 1990's when screening was overused. At the same time, the real diseased fraction of the target screening population must have dropped down to its historical minimum. In this study we do not aim to suggest optimal values for any of these variables, but would like to highlight the importance of having a better understanding of their dynamics.
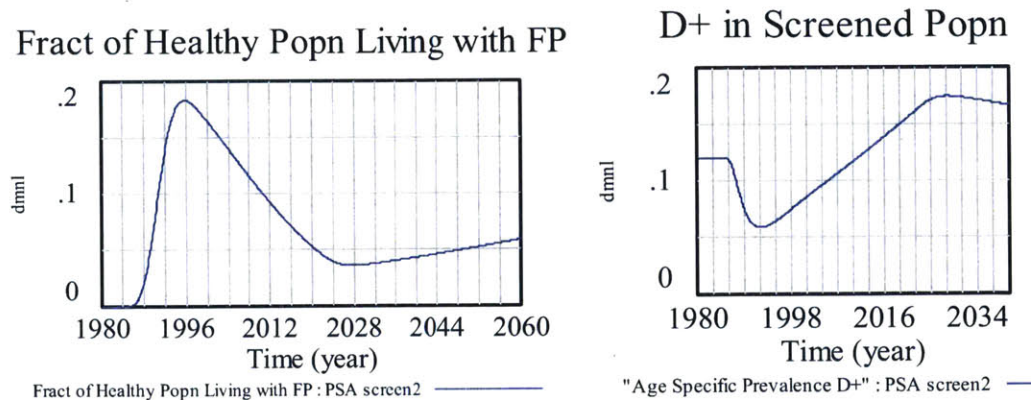
Figure 39 a) Fraction of healthy 35+ male population living with a False Positive test result b) Target screening population disease prevalence

Policy–relevant factors and analysis

"Cancer survivor" has different definitions in the literature. It commonly refers to any person who is diagnosed with cancer, from the time of initial diagnosis until his or her death. A more narrow

definition refers to subjects who only received primary treatment such as radiotherapy and radical prostatectomy. As of 2014 there were 14.5 million cancer survivors in the U.S., out of which 2.9 million were prostate cancer survivors. This survivor pool is expected to grow to 19 million by 2024 (DeSantis et al., 2014) due to aging, population growth, and improvements in early detection and treatment. Simulation results are close to the survivor data, and suggest a substantial increase to 5.2 million men in 2040, if current trends in treatment and screening were to stay constant. It also suggests that this value could be as low as 1.7 million in the absence of screening.

Cancer over-diagnosis also has several definitions. It refers to people diagnosed with indolent disease, and to those others who die of other causes and not of prostate cancer. This study uses the most conservative definition of over-diagnosis, where a screen-detected case is considered as over-diagnosed only if it is an indolent tumor. Existing estimates vary widely between 23%-66% (Hoffman and Zeliadt, 2010; Draisma et al., 2009). The base case simulation estimate is somewhere between this range on the conservative side, indicating that 24% of all diagnosed cases, and 33% of all screen-detected cases, are over-diagnosed, once the adoption trends have been stabilized.
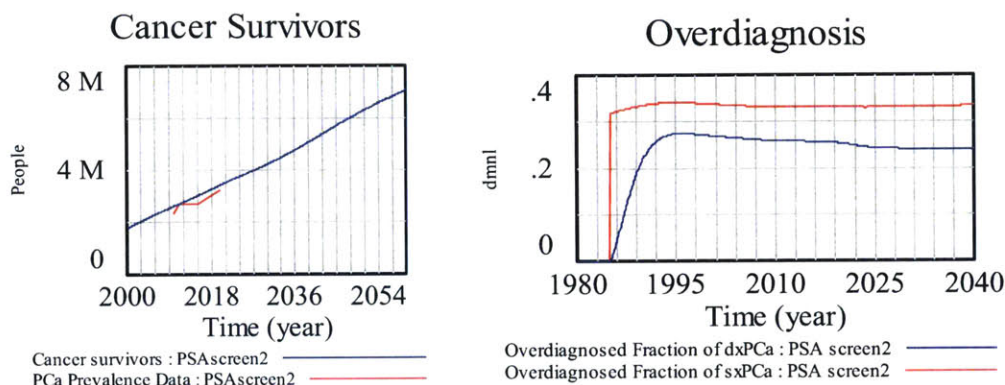
Figure 40 a) Cancer survivors, data versus simulation b) Size of the cancer survivor pool with and without screening

In Essay#1 we show that the recommended "formal" biopsy threshold for PSA testing stayed constant at 4 ng/ml throughout the initial years of screening dissemination; after which it starts to vary in the 2000's. The informal, "practice" threshold, however, has reportedly been lower than the formal one, suggesting poor compliance with recommendations. The real pattern for the average biopsy threshold is unknown, but it is generally accepted to be 2.5 ng/ml between 1990 and 2000 (Gulati et al., 2010). Also, Pinsky et al. (2005) have shown that biopsy frequencies of men with PSA's between 2.5 and 4 ng/ml were of the same order of magnitude as for men with a PSA higher than 4 ng/ml.

The "formal" recommended starting age to screen is shown to vary more than the biopsy threshold itself, both over time, and also between different guideline-issuing organizations. The actual starting age data is also not available, but it presumably follows the same pattern as the biopsy threshold, where formal indications first expand in early years of screening, and then start to narrow as harms and the evidence for harms accumulate over time. The base case simulation replicates this reference behavior of fluctuations observed in the screening criteria.

Threshold (Cutoff) Value

ng/ml

10

5

0

1980 1998 2016 2034
Time (year)

Threshold T[prof] : PSA screen2 ————
Threshold T[advoc] : PSA screen2 ————
Effective Threshold : PSA screen2 ————

Age to Start Routine Screening

years

50

40

30

1980 1995 2010 2025
Time (year)

Recommended Starting Age R[prof] : PSA screen2 ·
Recommended Starting Age R[advoc] : PSA screen2
Actual Starting Age for Routine Screening : PSA screen2

Figure 41 Base case simulation, threshold and starting age

Figure 26 shows the gaps between evidence and practice/advocate positions with regard to benefits and harms of screening. Advocates are assumed to start with a bigger initial positive bias for screening at the beginning of the simulation. The continuous expansion of criteria causes professional and advocacy opinions to gradually converge to an HBR value higher than 1, after which indications start to narrow. This causes an increase in biopsy threshold and the recommended age to screen, which is the current state of PSA screening. After a certain point, however, advocacy groups start to diverge again from professionals, and their perceived HBR decreases to values below 1, while it stays above 1 for professionals which suggests over-screening.

Perceived HBR T

dmml

2

1

0

1980 1998 2016 2034
Time (year)

Perceived HBR T[prof] : PSA screen2 ————
Perceived HBR T[advoc] : PSA screen2 ————

HBR New

dmml

1.2

1.05

.9

1980 1998 2016 2034
Time (year)

Pseudo HBR[prof] : PSAscreen ————
Pseudo HBR[advoc] : PSAscreen ————
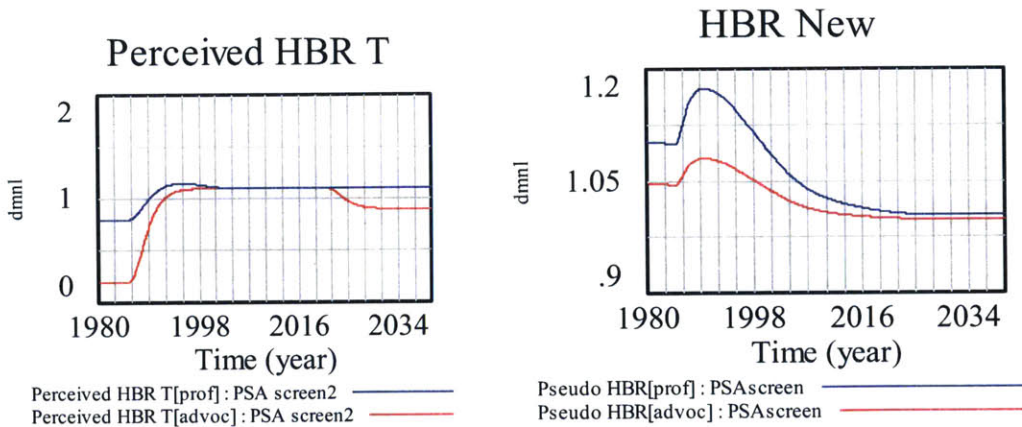
Figure 42 Base case simulation a) Perceived HBR and b) Pseudo-HBR

Effect of the HBR Translation Delay

Figure 27 shows the effect of changing the HBR translation delay (τ) on screening recommendations, as it is varied from 3 to 6 years. As τ increases, the undershoot in the effective threshold gets amplified, causing a bigger overshoot in the overall screened fraction, eventually leading to a higher fraction of healthy men to live with false positives and have unnecessary biopsies over the simulation time horizon.

118
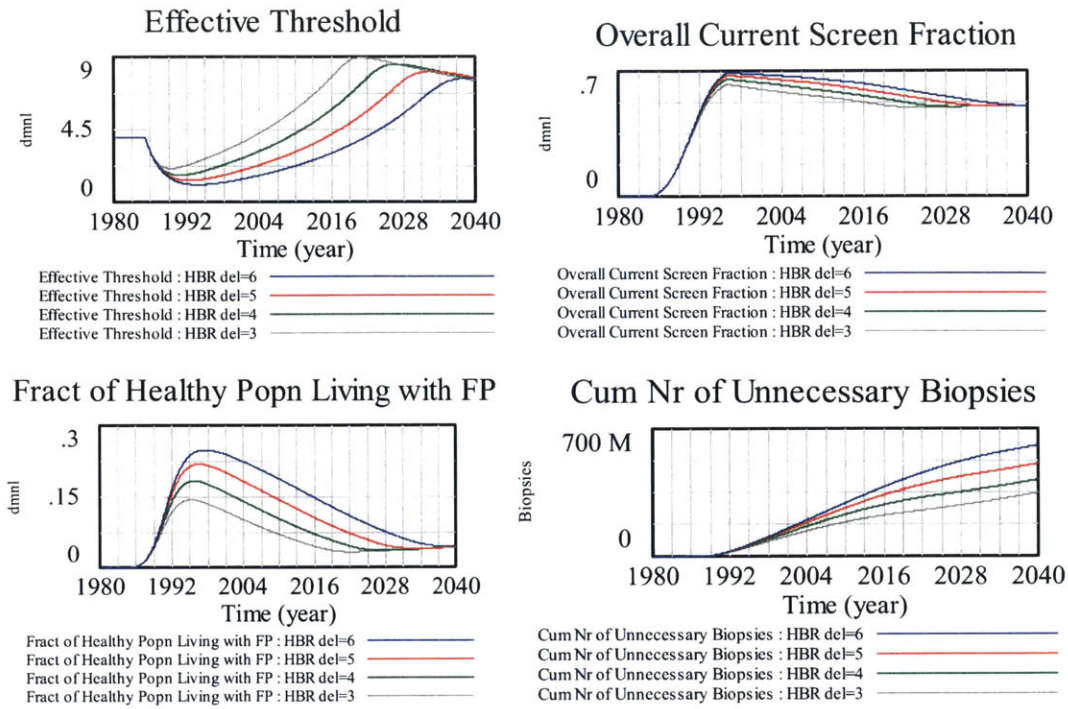
Figure 43 Effect of HBR translation delay

Figure 28 shows the effect of changing the maximum adoption fraction on over-diagnosis rate and cancer survivors, as it is varied from 0 to 100%. Maximum adoption fraction represents the maximum fraction of doctors who adopt the screening practice. As expected, higher adoption rates lead to higher over-diagnosis rates, and more cancer survivors.

Effect of Maximum Adoption Fraction
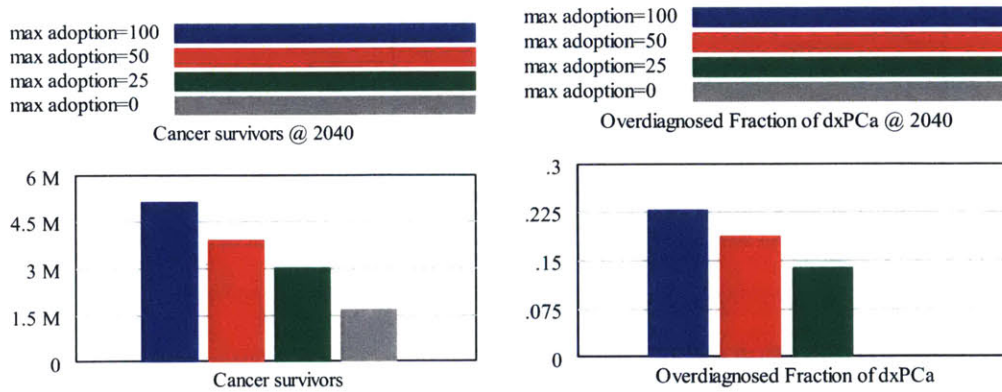
Figure 44 Effect of maximum adoption fraction on overdiagnosis and survivors

Effect of Harm Reduction Technology (HRT) on Screening Indications

Figures 29 and 30 show the effect of changing the HRT on screening indications. Four simulation results belong to different levels of efficiency for the HRT, varied from 0% to 100% (0%, 50%, 75% and 100%). When HRT is 100% efficient, treatments don't lead to any harm. It is seen that HRT potentially has a big impact on the dynamic behavior of the model and long-term trends in screening. As HRT becomes more effective, screening becomes more appealing and selection criteria get expanded. The efficiency of the HRT also has a big impact on the degree of overdiagnosis and the future number of cancer survivors.
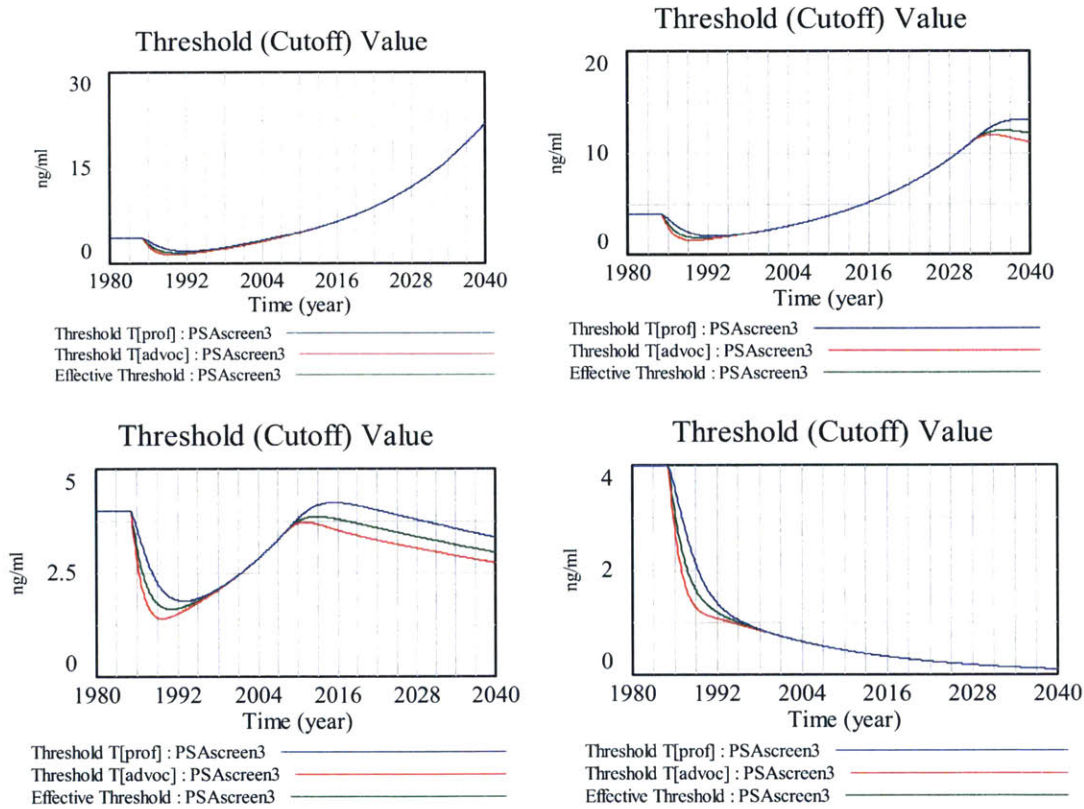
Figure 45 Effect of HRT on age to start routine screening

120

HRT=%0 effective		HRT=%0 effective	
HRT=%25 effective		HRT=%25 effective	
HRT=%50 effective		HRT=%50 effective	
HRT=%75 effective		HRT=%75 effective	
HRT=%100 effective		HRT=%100 effective	

Overall Current Screen Fraction @ 2040 — Overdiagnosed Fraction of dxPCa @ 2040

Overall Current Screen Fraction — Overdiagnosed Fraction of dxPCa
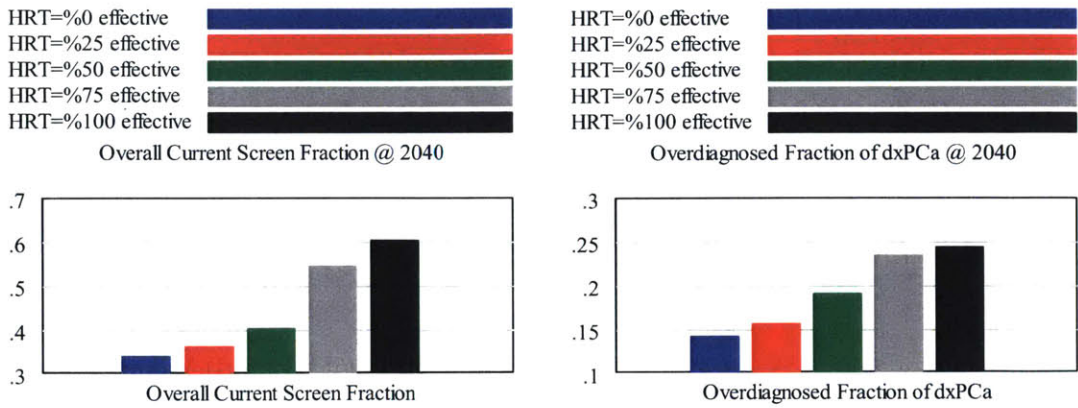
Figure 46 Effect of HRT on overdiagnosis and cancer survivors

Parameter Set Exploration

Several types of sensitivity tests are conducted on the model by exploring the parameter space. Monte Carlo simulation, also known as multivariate sensitivity simulation (MVSS), is used to automate the sensitivity analysis. In each of the cases below a subset of parameters is chosen to see how it changes the dynamic behavior of the model, given certain ranges.

Effect of Disutilities on Perceived Harms and Benefits

The disutility parameters including the biopsy disutility, utility decrement of living with treatment, disutility end of life, and biopsy compliance are varied within the ranges provided in Table 3. In most of the simulations, both advocacy groups and professionals agree that harms exceed benefits; whereas, in a subset of populations, advocacy groups diverge from professionals, trying to decrease the threshold and starting age to screen.
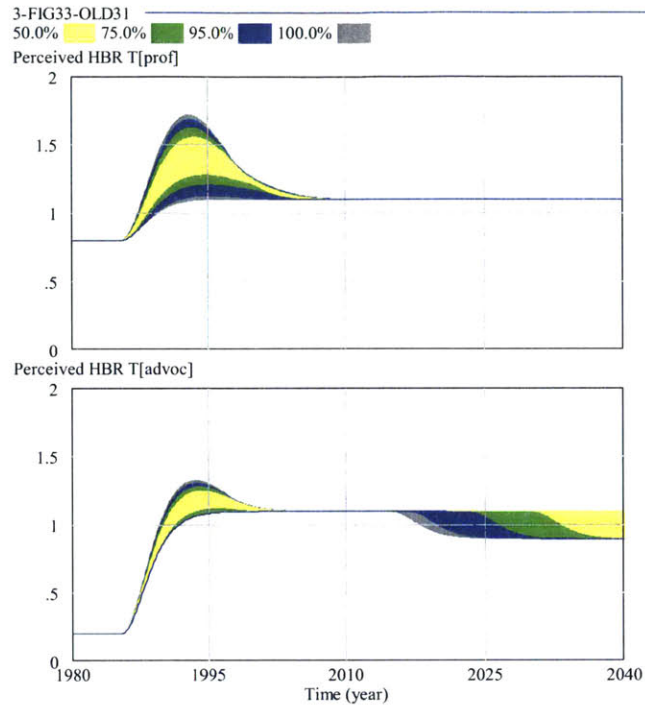
Figure 47 Varying disutilities for health states

The parameters biopsy compliance, maximum adoption fraction, and the HBR translation delay are varied within reasonable ranges. Biopsy compliance varied between 0-0.7; HBR translation delay varied between 2-10 years, and the maximum adoption fraction varied between 0.25-0.75. Figures 32 and 33 show the sensitivity graphs for the HBR, actual starting age to screen, and effective biopsy threshold.

122
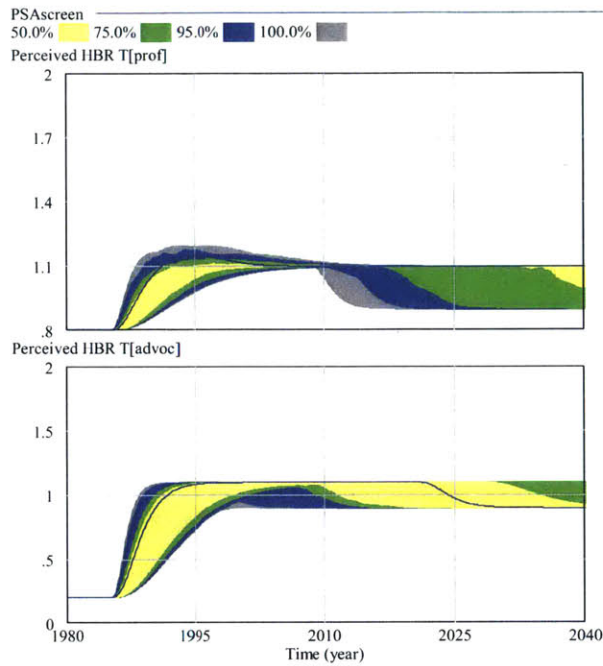
Figure 48 Perceived HBR$_{advoc}$ and HBR$_{prof}$
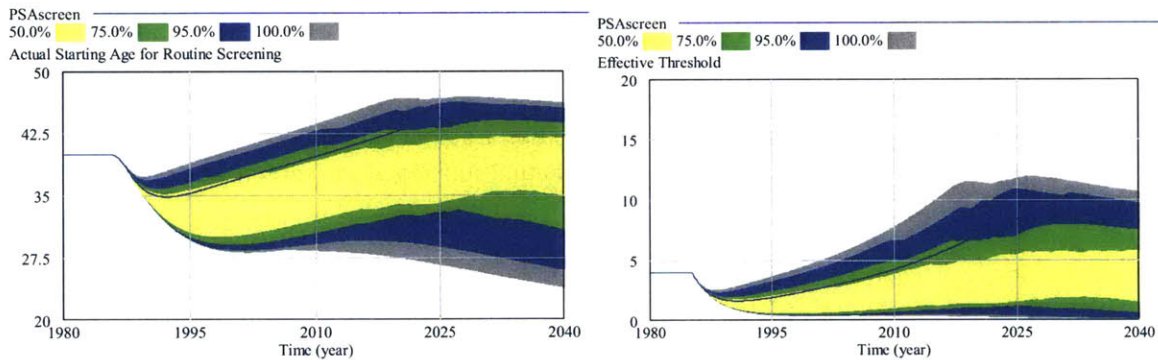
Figure 49 Actual starting age and effective threshold

Limitations of this study/ data

The results of this study rest on several key assumptions. First, as with any other natural history model, we make assumptions about disease onset, progression, and diagnosis in the absence of screening. Second, we assume that disease incidence remains constant at pre-PSA levels after 1987. Third, the model assumes that baseline prostate cancer survival remains constant in the PSA era.

We use data from a variety of sources that are subject to limitations. Although SEER is the most authoritative resource for information on disease incidence and survival in the U.S., it lacks estimates of prostate cancer survival in the absence of screening for the PSA era.

123

Data on some key indicators such as the actual biopsy threshold used in clinical practice and the actual recommended starting age are not available. We used data from expert opinions and published medical literature to justify model propositions.

Another simplifying assumption is that men are not subject to mortality harm because of treatment-related procedures, which may lead to overestimation of screening benefits. Moreover the harm reduction technology (HRT) reaches its maximum value of 1 very early, and as HRT reaches its maximum level its effect on treatment harms reaches a lower bound. A better way to model this would be to allow HRT to continue to improve over time.

We assume a constant clinical detection hazard in the base case, which may lead to overestimation of screening benefits. In fact, clinical detection rates may also have increased over time because of increased disease awareness in the PSA era.

Immigration data was not available by age group, and was assumed to be distributed proportionally between age groups, yet it may have implications for population aging.

No historical data was available for some other variables, including the fraction of healthy men with a false positive or true negative, or the progress of harm reduction technology.

And finally, trying to quantify the non-quantifiable puts a limit on the reliability of simulation outputs. However, the focus of this study was on causal structure and dynamic behaviors rather than point-prediction for key indicators.

Contributions of this study

The main contribution of this study is revealing the causal structure that generates fluctuations in screening criteria, and to explain the phenomena of over-screening/overtreatment that are not corrected by evidence. We develop and test an endogenous theory for population screening that generates fluctuations in guidelines, and leads to over-screening that cannot be attributed solely to available scientific evidence or to practice recommendations. To our knowledge, this is the first endogenous theory for guideline development that takes into account the inherent delays in guideline development and dissemination, bounded rationality, and the effect of multiple decision makers on key outcomes. By modeling the differences in formal and actual thresholds and multiple guidelines, we show how they may cause suboptimality in screening utilization.

Oscillations are shown to be natural to this class of problems due to inherent delays and bounded rationality in evidence-based screening, leading to long periods during which guidelines are suboptimal. This suboptimality may become persistent due to additional reinforcing feedbacks that may overwhelm evidence, which are introduced by the information and feedback asymmetry caused by indolent disease, and differences between evidence based and specialty groups.

The model endogenizes variables which are mostly taken as constants in other studies. These include the breadth indications of screening (including the biopsy threshold and the starting age to screen), the prevalence of disease in the screening population, sensitivity and specificity, and the harm reduction technology. It also separates the formal decision thresholds for screening from the decision thresholds that are actually implemented, showing their interdependency to each other as well as to the diagnostics of the test.

For example, existing studies usually assume a constant PSA level as the trigger for biopsy, which stays constant over time; but this is not an accurate reflection of the clinical practice. Endogenizing such variables allows us to show how they are changing over time, affecting the target screening prevalence, and hence the screening diagnostics themselves, which are also taken as constants in most studies. Since the test diagnostics are directly derived from the underlying probability distributions for diseased and healthy people, the model can as well be used to estimate the real prevalence of disease. Addition of an "indolent" disease category also facilitates the making of inferences about the real occult disease prevalence in the population.

We show that broad boundary feedbacks are more important than focusing on parameter values such as the biopsy sensitivity, and need to be included in future studies and in the actual guideline development process. Existing studies largely ignore broad boundary feedbacks, and including important delays in the system. Likewise, they also neglect the dichotomy between professional and advocate groups, which affects the perceived harms and benefits environment for screening, creating additional feedbacks that undermine reliance on evidence.

Another contribution of this study is the introduction of a more realistic structure for routine screening that allows keeping track of critical stocks that have been generally overlooked in previous studies: men with false positives and true negatives. We show that the fraction of healthy men with a false positive increases by age and varies between 5 and 20%, depending on screening criteria. The stock of men with a false positive is also a potentially important policy variable that needs to be taken into account.

This model is not primarily designed for making inferences about optimal screening policies, but can inform modelers and policy makers about potential levers in the system, and be used as a complement to existing modeling studies designed for optimization.

Simulation models like ours are tools that can aid healthcare professionals and policy makers in making complex decisions. They can provide constructive insights and dynamic intuition to supplement the typical empirical evidence for updating cancer screening recommendations; can offer a formal means to improve the development and implementation of evidence-based screening; and can help to relieve the public resistance against frequently changing recommendations.

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Appendix A. Prostate Specific Antigen (PSA) screening timeline in the US, with major event
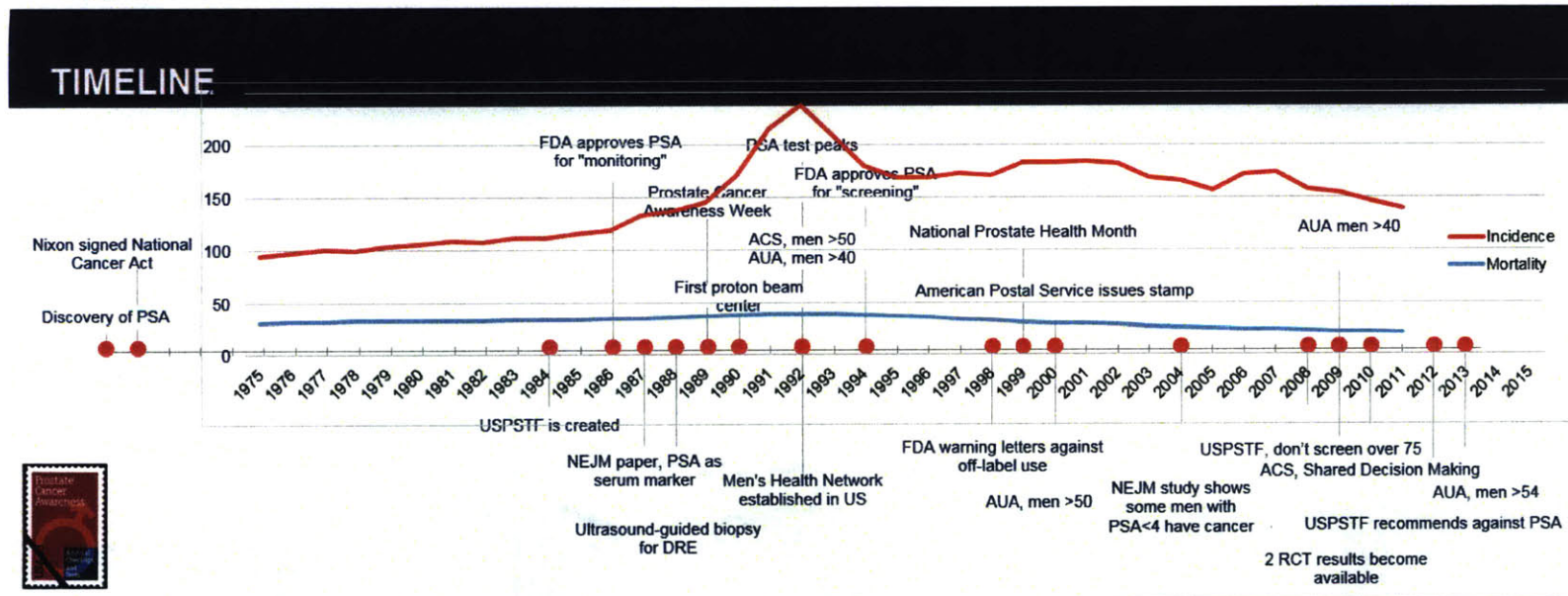
Figure 16 PSA timeline with selected major events, red and blue lines show prostate cancer incidence and mortality trajectories per 100.000 men

Appendix B. Recommended Starting Age to Screen, 4 major guideline issuing organizations

Professional Body	PSA Screening Guidelines for Early Detection of Prostate Cancer																								
Year of Release	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total # of Updates
US Preventive Services Task Force (USPSTF)																		don't screen 75+				don't screen			2
American Cancer Society (ACS)		50+					50+				50+					50+				SDM at 50				SDM at 50	9
American Urological Association (AUA)		40+								50+									40+				55-69		4
National Comprehensive Cancer Network (NCCN)		40+					40+						50+							45 BL=40			45 BL=40		7
																									22

Figure 17 Summary of Major PSA Guidelines for 4 major professional organizations

131

Appendix C. List of Interviewees

Name	Date of Interview	Occupation	Primary Category
Emily Hartzog	1/23/15	MD, Ob/Gyn, outreach and writer	Clinician
Marla Eglowstein	8/18/15	MD, Ob/Gyn	Clinician
James Michaelson	2/4/15	PhD, Director Mass General lab for Quantitative Medicine, on American Cancer Society (ACS) guideline committee for 3 years	Policy, Academic
Blake Cady	1/16/15	MD-PhD Emeritus, Surgeon Oncologist, former member or American Cancer Society (ACS) tumor board	Academic, Policy
Harry de Koning	2/15/15	Professor of Evaluation of Screening, Biochemistry and Pharmacology, CISNET comparative modeling group, PI of prostate cancer modeling group	Academic, Policy
Navid Ghaffarzadegan	1/23/15	PhD, Professor, Virginia Tech, Industrial and Systems Engineering	Academic
Ilker Tinay	2/5/15	MD, Surgeon-medical urologist, Marmara University School of Medicine, Previous: Brigham and Women's Hospital, Urology, Research Fellow in Surgery,	Clinician, Academic
Confidential	2/17/15	Confidential interview with patient and relative	Patient
Oguzhan Alagoz	1/22/15	PhD, Professor, UWM College of Engineering, Industrial and Systems Engineering, Cancer Intervention and Surveillance Modeling Network (CISNET) by National Cancer Institute (NCI)	Academic, Policy
Deborah Kotz	2/18/15	Press Officer at FDA, Previous: Freelance, Boston Globe, US News and World Report	Media-Science Writer
Bilge Aktas	2/22/15	MD, Research Scientist, Yale University School of Medicine, Medical Oncology Department, Division of Breast Oncology	Clinician, academic
Anonymous	2/23/15	Media, Science Reporter	Media-Science Writer
Nancy Keating	2/27/15	MD, PhD, Division of General Internal Medicine, Brigham and Women's Hospital, Department of Health Care Policy, Harvard Medical School	Academic
Natasha Stout	3/2/15	Professor, Harvard Medical School	Academic, Policy

Anonymous	2/27/15	MD-PhD, Academic and Clinician	Policy, Clinician
Anonymous	3/9/15	MD, Pathology	Clinician, Policy
Anonymous	3/10/15	Patient Advocacy Group	Advocacy Group
Confidential	3/12/15	Confidential interview with cancer patient's family	Patient
Karuna Jaggar	3/12/15	Executive Director, Breast Cancer Action	Advocacy Group
Anonymous	3/16/15	Patient Advocacy Group	Advocacy Group, Patient
Richard Ablin	2/19/15	Professor of Pathology, U of Arizona College of Medicine	Academic
John Barry	3/16/15	MD-PhD, Professor in Urology at OHSU, former president of the American Urological Association (AUA), and the American Board of Urology	Clinician, Academic, Policy
Peggy Orenstein	3/17/15	Media, writer, Journalist at NYTimes	Media- Science Reporter, Patient
Erin Hofstatter	3/9/15	MD-PhD, Yale School of Medicine, Assistant Professor of Medicine (Medical Oncology) and Co-Director, Genetic Counseling Program	Clinician, Policy
Deanne Attai	3/24/15	MD, Former President at American Society of Breast Surgeons, Assistant Clinical Professor of Surgery UCLA	Clinician, Policy
Lajos Pusztai	3/26/15	MD-PhD, Yale School of Medicine, Chief of Breast Medical Oncology, Co-Director of the Yale Cancer Center Genetics and Genomics Program	Clinician, Policy
Peter Juni	3/24/15	MD-PhD, Director, Applied Health Research Centre, St. Michael's Hospital, and Professor of Medicine, University of Toronto. Previous: University of Bern, Director of the Institute of Primary Health Care, Professor and chair of Primary Health Care and Clinical Epidemiology in the Faculty of Medicine, Switzerland	Academic, Clinician, Policy

Shelley Justa	4/8/15	MD, Family practitioner for 30 years, American Board of Family Medicine	Clinician
Gayle Sulik	4/7/15	MA, PhD, Research associate at the University at Albany (SUNY) and founder of the Consortium on Breast Cancer	Academic, Advocacy Group
Liane Philpotts	4/16/15	PhD, Professor of Diagnostic Radiology and Chief of Breast Imaging at Yale Med School. Radiology, diagnostic radiology	Clinician, Policy
Matt Gillman	5/4/15	M.D., S.M. Director, Environmental Influences on Child Health Outcomes (ECHO); Office of the Director, National Institutes of Health.	Policy, Academic
Teresa Corr	9/2/15	Science Writer at Consumer Reports	Media, Science Reporter
Gary Schwitzer	9/3/15	Publisher, HealthnewsReview.org, Adjunct Associate Professor, UMN School of Public Health	Media, Science Reporter, Academic

Appendix D. Recruitment Email
Request for an Interview on Dynamics of Routine Health Screening in the US

Dear Professor XX XX,

I am contacting you to ask for an appointment to have an interview with you on our research study, conducted by **Professor John D. Sterman and myself,** from the Sloan School of Management at the Massachusetts Institute of Technology (M.I.T.) We are investigating the dynamic trends in screening for cancer in the US, including the roles of the evidence base, translation and risk communication. We seek to understand sources of variation in screening guidelines and the actual practice.

We identified you as a possible participant in this study because of your expertise in and knowledge of issues related to the research objective. We believe you can help inform our understanding of the issues in important ways.

This interview is voluntary and you have the right not to answer any question, and the **information you tell us will be confidential** unless you give us permission to use your name, title, and / or quote you in any publications that may result from this research. We expect that the interview will take about 45-60 minutes, or less. The results of this study will be included in my doctoral dissertation, and published in a journal that can be shared with the participants upon request.

We would greatly appreciate your participation in this study. Please do not hesitate to contact me if you need more information before deciding whether or not to participate.

Best regards,
Ozge Karanfil

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Appendix E. Main Interview Outline

INTERVIEW OUTLINE

Dynamics of Routine Health Screening
February 2015

Interviews will be semi-structured, and vary according to the particular knowledge of the interviewee.

The following general outline will be followed:

I.   **Informed Consent**

II.   **Project Background**

III.   **Background of Interviewee**

    a. Role (medical professional, health policy, clinician/ practitioner, other)

    b. Role in screening policy, clinical practice and/or academia

    c. Who else should I talk to?

IV.   **Questions related to the study (as appropriate to the interviewee's knowledge)**

    a. In your opinion, what are the major determinants for how much screening happens?

    b. Do you think are there any situations where people are screened too little/too much; or too early/too late?

    c. Do you think PSA testing and/or mammography is overusing or underused, or both?

        i. If overused, what are the possible reasons?

        ii. If underused, what are the possible reasons?

    d. Which factors do you think contributes most to doctor's decisions on screening?

    e. Who makes the decision of screening mammography in a primary care setting? Doctor, patient, any others who contribute?

    f. **As a medical/ healthcare professional/policy maker/ academic** can you describe your own views on the importance of mammography and/or PSA testing? (If applicable)

        i. What are your views of existing screening guidelines?

        ii. What are the most reliable information outlets for the general public/ clinicians?

iii. When do you think mammography/ PSA screening needs to start for patients who are in average and high risk groups?

iv. How frequent do you think they need to be tested?

v. What are the potential benefits of screening?

vi. What are the potential harms of screening?

vii. How do you think about benefits and harms?

viii. What do you think about the role of media? Advocacy groups?

g. **As a clinician/ practitioner,** do you recommend/prescribe routine testing? What are the criteria you use to recommend screening? (If applicable)

i. How do you make your decision?

ii. What else are you looking at (if any) other than screening results?

iii. Which treatment modalities do you recommend (If applicable)?

h. **As a clinician/ practitioner,** have your patients ever disagreed with your views? (If applicable)

i. Have you had an experience where your patient asked you for testing that you didn't think were appropriate?

ii. Have you had an experience where you suggested testing where your patient didn't think it was appropriate?

iii. How did you resolve the disagreement?

i. **As an individual** have you been screened/ had mammogram/ PSA test? Why or why not?

i. Can you describe your own mammography experience? (If applicable)

ii. Can you describe your own PSA testing experience (If applicable)?

iii. If you had received a high PSA test or positive mammogram, what would you do? (If applicable)

Cancer survivors, Feedback asymmetry, misperception of Feedback	*The challenging thing is that most women who get cancer diagnosed by mammogram think that the mammogram saved their life, whereas, you know, the evidence suggests probably about 13% of cases, that mammogram actually saved their life, that all the other cases would have been diagnosed clinically and still would have been cured. So there's a part of this is a misperception, that the mammograms are saving lives, when often the mammograms are picking up over-diagnosed cancers, or, you know, just finding cancers that would have been found in a month or two anyway on a clinical exam."—Nancy Keating, MD, MPH, Professor of Health Care Policy at Harvard Medical School*
	"It's really weird when you think about it. Women are, they've been made very, very afraid of breast cancer. Way more proportionately afraid of it than they should be. There's this whole idea of misfearing, which is fearing the wrong thing…Women's misfearings. Women ought to be really afraid of heart disease, right? That's what they should be afraid of, that's what's probably going to kill them. But they're super afraid of breast cancer because we've made everybody so damned aware of it with the pink ribbon first of all, and secondly because we've created this whole new class of survivors through mammography, the so-called survivors. So there's a lot of women who have had it all over the place all of a sudden, so it's much more seemingly prevalent, and there was an authentic rise of course of breast cancer in the '70s and '80s and '90s…"—Peggy Orenstein, Journalist, NYTimes
	"I was like, "What are you talking about? The life that was saved was mine. I am the woman whose life was saved by that under 50 mammogram and you need to know who I am," so that was why I wrote my first article."—Peggy Orenstein, Journalist, NYtimes
	"Yes, would have progressed if they hadn't had the mammogram. We don't know how to know that yet. But anyway, there's definitely people around who are calling themselves breast cancer survivors who had something that did not need treating, and now are here to tell the tale. That just further amplifies women's fears. Then you've got pink garbage trucks running around or whatever you've got, all the time now. So suddenly women began to believe that breast cancer, going from something that nobody ever spoke of in 1970 to something that nobody would shut up about [laughs] years later, was a huge change in the culture, not having anything to do with medicine."—Peggy Orenstein, Journalist, NYtimes
	"Honestly that's the problem, is the headlines just reduce it to one sound bite. It's a combination of factors. I think honestly part of it now is because breast cancer is so common. Everyone knows someone that's been treated, everyone knows someone that's had a recurrence. I think as a society we have less tolerance for inconvenience, and that just evolved over time. So people have the idea, "I just want to get it over with and get it done, and get back to my life." We live in a very, "I want it now," and disposable society. I think that has something to do with it as well."—Deanne Attai, MD, Former President at American Society of Breast Surgeons, Clinical Professor of Surgery UCLA
	"There are two different perspectives: The individual one, and then the sort of public health one, and quite often you will hear people say, "Screening saved my life, and so it's worth it for everyone." —Media, Science Reporter

"I think breast cancer is for some reason a very emotional topic, and it stirs emotion, so I think that drives it, a lot of the stuff about mammography. "This mammogram saved my life, so you should have one too."... I don't think they do, but that's what you hear and read, so you can't ever say obviously whether this one mammogram saved my life, but I think that's what a lot of stuff you read about in the advocacy or the general and so we think of course it's going to save my life. It's a screening test and it's going to catch it early." — Natasha Stout, Professor, Harvard Medical School

"It was January 1997 when I was diagnosed [with breast cancer]. So I don't think that people really...I definitely didn't understand the politics around screening and it took me a long time to understand that fully. My first article was really just about being a young woman diagnosed with cancer, and it was in fact the diametric opposite of what I wrote in 'Feel-Good War Against Cancer' because they had just had one of the studies out that showed that there was no real reason to be doing mammograms on women under 50. The way that it was put was that it didn't save enough lives. The way that's it put, I think is a problem...It just sounds hostile to women. But anyway I was like, "What are you talking about? The life that was saved was mine. I am the woman whose life was saved by that under 50 mammogram and you need to know who I am," so that was why I wrote my first article. Also because of the particular complications of being a 35 year old with cancer, I hadn't had children and I wanted to have children, and what was this going to mean. So there was a particular story that I thought I had to tell at that point and I wrote a cover story for the New York Times Sunday Magazine at that point, that was called '35 and Mortal' I think. It was like the diary of a young woman with breast cancer. When I look back on that story now, it has pretty much everything in it that now bugs the crap out of me about stories about breast cancer." —Peggy Orenstein, Journalist, NYTimes

"But anyway, there's definitely people around who are calling themselves breast cancer survivors who had something that did not need treating, and now are here to tell the tale. That just further amplifies women's fears. Then you've got pink garbage trucks running around or whatever you've got, all the time now. So suddenly women began to believe that breast cancer, going from something that nobody ever spoke of in 1970 to something that nobody would shut up about years later, was a huge change in the culture, not having anything to do with medicine." —Patient Advocate

| **Feedback Asymmetry** | *"People are very nervous of breast cancer. If you ask women what they die of its not cardiovascular disease, they think they die of breast cancer. It's the scariest thing out there for women. I think that some of that is obviously mammograms and getting back these reports that are worrisome, but a lot of it's just what they're hearing."* —Clinician

"There's a lot of perpetuation of breast cancer survivors as heroes...It's really done a disservice to breast cancer. So watching that roll out, watching the rise of the pink ribbon culture I guess is what really began to make me angry, watching this focus on people who weren't going to die anyway being hailed as heroic for getting a disease and surviving what they were going to survive anyway, and watching other people die, was breaking my heart. So watching these two ends of the spectrum..." —Peggy Orenstein, Journalist, NYTimes |

Anecdotes	*"We all know cases where people would not have had their disease detected if they hadn't been screened early. It's not necessarily proven that they would not have survived without that screening. We can't know that for an individual, and studies of many individuals can be misleading because of biases like lead time bias and length bias. What many people respond to, however, are anecdotes. You hear about a women whose breast cancer was detected by mammography in her 30s or 40s, or PSA in a younger man that can seem pretty compelling. And anecdotes are really powerful, in fact we learn a lot from anecdotes and anecdotes are really important. But they're only one small piece of evidence and not usually the most useful piece of evidence. I think anecdotes drive some screening that's not necessarily warranted..."*— Matt Gillman, M.D., S.M. Director, Environmental Influences on Child Health Outcomes (ECHO); Office of the Director, National Institutes of Health
Visibility	*"So if you look in the mammography trends, screening trends, or if you look at actual cancer incidents, they're different. There's the Betty Ford bump, of when Betty Ford, she was the wife of Gerald Ford. So when she was diagnosed with breast cancer, there seems to be like a little bump in incidents, and I think the same is true for colorectal cancer, when Katie Couric had a colonoscopy on TV, or something, talked about it on TV, because I think her husband died of colorectal cancer..."* — Natasha Stout, Professor, Harvard Medical School
Lack of Time	*"I think many doctors just have individual thoughts and ideas about that, and that plays a role, and that is why I think national programs like in the European countries where people are just invited independent of the physicians, it's very helpful in the sense that it gives you the correct information, and you can decide on your own. That's how in many European countries it's being done....Of course the issue you cannot elaborate what your doctor mandates, but the question is, do many-- is there enough time for people to do that? I'm not sure about that".* - To have the interaction with your physician, and talk about the harms and benefits. Of course, that would be quite ideally that there is also a physician involved, but I'm not sure whether there's enough time in the physician room to do that correctly, and that is why I think national programs like in the European countries where people are just..."* — Harry de Koning, Professor of Evaluation of Screening, CISNET
Lack of Thinking of Long Term Consequences	*"But I think what you cannot see as you make these initial decisions, because you're making them in the context of emotional turmoil, is what the long-term impact is. When you get a positive mammogram or a positive PSA, I don't think you're wondering about your sexual health 10 years from now, for example."* — Patient, Patient advocate
Risk Averseness, Handling the Uncertainty	*"It's, I mean, for an individual, they might say it doesn't matter to me. I just want to be safe. I don't care if it's unnecessary. I don't want the risk. I don't want to live with that risk....And people have trouble understanding just how big the risk is. I think any mention of cancer is scary, very scary..."*—Reporter, Science Magazine

"The women that I spoke to were not thinking Angelina Jolie. It could have been in their minds, but that's not at the top of their mind. I think many of them were guided by family members and loved ones who were like, "Why wouldn't you do everything you could to not have this cancer again?" Even if they-- they're not necessarily persuaded by clinical trials. It's interesting, because doctors are the same way. I mean, speaking with the professors and oncologists, they were telling me many of |

their patients who were choosing mastectomies with early-age breast cancers were physicians, were oncologists, were radiation oncologists. These are people who don't trust their own therapies to keep their cancer at bay that they were getting mastectomies. They don't trust the clinical trial saying it doesn't make a difference."
—Deborah Kotz, FDA Reporter

"My mom was like, "It [insurance] covers it [mastectomy]," even though she had all these doubts she was, "It's probably better than I just get rid of the possibilities of getting cancer in the future," and she kept on reminding herself that because I guess she needed some justifications as to why this is good for her, so I think she kept on reminding herself with that." —Patient Relative

"Yes,, I think this whole system is-- and this theory of mediation is adding to that. But more of fear of mediation, this whole thing that, "Well, I don't want to miss the disease. I don't want to be bad, so I will do extra, extra stuff." — Oguzhan Alagoz, Professor, Industrial and Systems Engineering, University of Wisconsin-Madison, Cancer Intervention and Surveillance Modeling Network (CISNET)

"I also say, "The other thing I want you to think about is how you would feel if you don't have a mammogram and you get diagnosed with breast cancer, and it's an aggressive cancer. How would you feel? Would you have regret of thinking, what if there's something I could have done?" And if people can look at me and say, "I can handle that. I'm fine. I, you know, I don't like overtesting. I get the over treatment and the overdiagnosis." Then I'm like, "Let's not do it." If people look at me and say, "Oh, I could never live with myself if I thought there was something else I could have done," then I'm like, "You should just get a mammogram," because the risk that that's going to be the case is extremely low, but some people just can't handle that uncertainty..." —Nancy Keating, MD, MPH, Professor of Health Care Policy at Harvard Medical School

"I think that, yes, when you talk about the drawbacks and benefits of screenings, women are much more afraid of a cancer that is undiagnosed than having a screening and having the biopsy. You know, I'd rather have that knowledge and have that control than, you know, be thinking about cancers that I'm not doing. And once I do wind up with a cancer, and its not-- and I could have caught it earlier. So, yeah, and it's the same thing, when they choose to have a mastectomy versus a lumpectomy, that many of them don't want the anxiety of having to go back for all these screenings and having to worry. They'd rather just know they did everything they could to get rid of every breast cell they have in their body as much as they could." —Deborah Kotz, FDA Reporter

Understanding Uncertainty	*"Actually, in Science Magazine, I was very lucky at Science Magazine. You don't get that kind of pressure. I did not. Have any trouble there. I think the difficulty is trying to get sort of readers, the public, interested in understanding these fine differences in risk. People don't want to talk about risks in that detail. Most people say, "Yeah, if there's cancer, let's get me away from it." So I think that's the challenge, is trying to get people to think about the degree of risk, and how to evaluate it for themselves. It's very difficult..." — Media, Science Reporter*
Lack of rational thinking?	*"You see, nobody suggested that human societies act reasonably, it's [overuse of screening] completely absurd. We will have very soon one screening, it's exactly as you say, one screening measure, one screening intervention, that's flex sigmoidoscopy, that works, and it's implemented. But what is implemented most is mammography, problematic, and it's being followed by opportunistic gray PSA*

	screening. So basically we failed as a society to act reasonably, yes."—Peter Juni. MD-PhD, Director, Applied Health Research Centre, St. Michael's Hospital, and Professor of Medicine, University of Toronto, Previous: University of Bern, Director of the Institute of Primary Health Care, Professor and Chair of Primary Health Care and Clinical Epidemiology in the Faculty of Medicine, Switzerland
Availability	*"If you want to ask some specific questions, I think PSA and mammography screening, it has been overused. I think, I don't know if it was ever underused, because it wasn't that much available in the beginning, but certainly it's everywhere now I think…"—Clinician*
Celebrity Effect, Visibility	*"I think that the media and the celebrity effect, as I've written about, is a bit of a problem. It's a bit of a problem because women then get the sense that it's no big deal, you just go have your breasts removed and then you're back doing your normal thing, and it's no big deal. Nobody sees Angelina Jolie on the first day after surgery when she's in pain and has drainage tubes and all that sort of thing." —Deanne Attai, Former President at American Society of Breast Surgeons, Clinical Professor of Surgery UCLA*
	"Unfounded beliefs resulting from manipulative persuasion, e.g., advertising, "awareness" campaigns, product placements, celebrity stories, fearful doctors, misplaced faith in medical technology, fear surrounding disease, overestimation of risk, tradition." —Gayle Sulik, Research associate at the University at Albany (SUNY) and founder of the Consortium on Breast Cancer
Specialty Perspective	*"The doctors believe that that should be done because in their practice they've seen women get diagnosed via mammogram. So that becomes their personal anecdote experience. My aunt is in her 80s, she's got some very significant health related issues. Her doctor is bugging her to get annual mammograms. My aunt wrote to me after that piece was published and she said, "My doctor wants me to get a mammogram and I told her what your piece said and she said, 'No, you have to get a mammogram every year.' " I wrote back to her and said, "First of all, change doctors. Secondly [laughs] you're in your 80s, you have a chronic health condition. You are not going to die of breast cancer. Stop getting mammograms." It's like a drag for her go in, there's no reason for her to go in. It's ridiculous…" —Clinician*
	"I think at tumor board we sometimes see the outcome of too little too late. So yes, I think there are sad stories where someone just didn't go in for their mammogram for a couple of years and it comes back with this tumor. I think there are probably situations where people screen too much, but I think that it's hard to know what those are and I think that's what some of these public guidelines are trying to get at. I think, say patients are screened and they find a little lesion on a mammogram, and then a biopsy's done, and then the pathologist isn't sure whether it's absolutely benign, and then there's a surgery done. So you could argue for that patient, she had an extra biopsy, she had an extra surgery because of the screening. So I think those are two sides of the coin. I'll admit my bias that I'm a pathologist and I've seen the bad things that happen, that I'm pro screening if you want to know my bias." —Clinician
	"I'm not involved in, let's say PSA testing in the lab. But I kind of see the back end of screening, I'm not involved in anything. I don't see patients directly, I don't

	recommend this testing, I just see the outcome once the patients get diagnosed or the results of their delay in diagnosis." —Clinician
Concept non-intuitive, hard to grasp	*"Well first of a lot of is about belief. Basically it seems to be a good idea to early detect an invasive cancer and people all have to believe that since this seems such an obviously good idea it must be good. Then they tend to ignore the evidence entirely, or they have excuses why the evidence... [from a] randomized trial is not showing what they expect."* —Peter Juni. MD-PhD, Director, Applied Health Research Centre, St. Michael's Hospital, and Professor of Medicine, University of Toronto *"Barbara [Brenner, former president of Breast Cancer Action] was really the person who started saying to me, "You've got to look at the screening thing, you've got to look at the screening thing, you've got to look at the screening thing," and she would explain to me what the issue was and I kind of couldn't grasp it. I kept saying, "It's got to be better to find it earlier," she's like, "Well sometimes, sometimes not," and it took me really a long time to wrap my mind around what....it doesn't make sense....It just was so hard to understand it. The same thing happened to me when I wrote my article. I kept trying to explain it to my editor and she kept saying, "Yes, but..." and I go, "Well no, because of this, this and this." I felt like if I could get it across to her and then when I finally got it to her it got bumped up to the next editor up, who weeds everything. There were two top editors who read everything in the magazine. Then she said, "Yes, but this doesn't make any sense," I go, "No, it really does." —Peggy Orenstein, Journalist, NYTimes*
Fascination with New Technology	*"So I think there are a lot of professional reasons and just human, emotional reasons for the boom in screening. Plus, these companies are coming out with better and better and more sophisticated technologies, which always appeals to us Americans."* — Media, Science Reporter *"Do you think that it's that people don't know that screening doesn't always work? It's not a perfect test. Mammography's not. So maybe we don't have that understanding. I think it's going to help me. It must help me, if they're recommending it."* — Natasha Stout, Professor, Harvard Medical School
	"We were very involved into decision making. So nobody forced us to make a particular decision, but what was difficult for us was sometimes to understand the motivation behind surgeons insisting on particular options. As I told you before, two different surgeons insisted on going with two different options, but it was really difficult for us to figure out what their motivations were behind this insisting. As at last, we didn't look at this. We just wanted to continue with our own instincts." — Patient and relative

APPENDIX G. Risk Perception and Fear

Academic	*"I think the major determinants are, I think, the commerce and industry and the perception of the public. That's not the case in Europe. I think in the US, I think these are, let's say, quite important. I believe in evidence. This is my major role and my major career, but I certainly believe in evidence. I think in many instances it is number one, certainly evidence-based, doing trials, doing quantification, and cost-*

effective itself, so it should be number one, but because you especially asked about how much screening is going on, and I think in the US, I think these public perceptions and industry are forcing it to do play a major role, I think, yes." — Harry de Koning, Professor of Evaluation of Screening, CISNET

"Fear....No, I say fear and money. Scaring people, scaring them and making money from scaring them ...What happened is that [in 1986] everybody started to use this test to detect prostate cancer. The way they did it was they spread the word that prostate cancer was increasing, the incidence was increasing. The reason why the incidence was increasing, because they were using the test. So the whole idea was here, that with fear, you scared, you told patients, "You have to have a PSA test because prostate cancer will kill you. If you have a PSA test we can detect the disease early enough so we can treat it and we can cure it." So that was the driving force, was fear. The fear drove the patients to get the test..." — Richard Ablin, University of Arizona, College of Medicine, Professor of Pathology

Policy, Clinician	_"Fear of cancer. Opinion about the primary care physician. Fear on the part of the patient for treatment side effects. Concern on the part of family and spouse about undetected cancer, untreated cancer, or improperly treated cancer. Healthcare cost, and access to healthcare... For instance if you live in eastern Oregon you're six hours away from a major medical center where you could have a radical prostatectomy." —John Barry, Former President of the American Urological Association and Professor of Urology and Professor of Surgery, Oregon Health and Science University_ _"People are very nervous of breast cancer. If you ask women what they die of its not cardiovascular disease, they think they die of breast cancer. It's the scariest thing out there for women. I think that some of that is obviously mammograms and getting back these reports that are worrisome, but a lot of it's just what they're hearing."— Clinician_
Advocacy/Activist Group	_"There's no question, fear of cancer. Other people have written about what cancer means culturally, that's the dread disease. Sure, yes, fear of cancer. That's a whole cultural analysis...I want to be very clear, that I do not think there is a single right answer. I think that fear is real and I think part of healthcare and wellbeing means acknowledging that." —Patient advocate_ _"...So I don't think women are wrong or uninformed for wanting to have mammograms. Each woman must navigate the benefits and harms of screening for herself, in a way that attends to her overall wellbeing. Which is situated within the culture that we live in, including fear of death and fear of breast cancer. Some women are terrified of breast cancer and for some of these women the risk of overdiagnosis, overtreatment, false positive, etcetera, those are pale in comparison to their fear." — Karuna Jaggar, Executive Director, Breast Cancer Action_ _"Most often, people are screened too much and this is not just about mammograms and PSAs but other diseases as well. We live in a fearful society in which risk of the wrong things keeps people primed to accept and even seek out interventions so that they we 'feel' safer even when they are not safer." —Gayle Sulik, Research associate at the University at Albany (SUNY) and founder of the Consortium on Breast Cancer_ _"Unfounded beliefs resulting from manipulative persuasion, e.g., advertising,_

	"awareness" campaigns, product placements, celebrity stories, fearful doctors, misplaced faith in medical technology, fear surrounding disease, overestimation of risk, tradition." —Gayle Sulik, Research associate at the University at Albany (SUNY) and founder of the Consortium on Breast Cancer
Patient	"There's so many people, guys we know whose PSA elevated, everybody gets freaked out." —Patient from the Documentary: The Second Opinion
	"...When you get the word "Cancer" as I said I heard it over the phone. The feeling I got the elevator stops, that's the feeling you get. And for a month I was a basket case. I'd go to the movies and I'd say this is the last movie I'm ever gonna see. I would go to a restaurant and I'd say this's the last meal I'm gonna ever have in that restaurant. My wife was astonished as I was. She's gonna lose her terrific husband...She was worried and said have it out." —Patient from the Documentary: The Second Opinion
	"I had a mammogram in my mid-thirties when my primary care physician panicked about a swollen lymph node in my right armpit. It was a frightening experience. The radiologist was annoyed because it seemed like overscreening even then. Clearly, there was nothing going on. But the doctor wanted 'to be safe, and so screened.' I now know better. I'm of screening age, but when my doctor asks me every year if I want the script, I say no. She understands. She knows the science. The hype surrounding screening, the push for screening now because it's institutionalized protocol, is unethical in my opinion and does more harm than good. I will never be screened with mammography technology again."— Gayle Sulik , Research associate at the University at Albany (SUNY) and founder of the Consortium on Breast Cancer
Media/ Science Reporter	"It's, I mean, for an individual, they might say it doesn't matter to me. I just want to be safe. I don't care if it's unnecessary. I don't want the risk. I don't want to live with that risk....And people have trouble understanding just how big the risk is. I think any mention of cancer is scary, very scary..."— Media, Science Reporter
	"It's really weird when you think about it. Women are, they've been made very, very afraid of breast cancer. Way more proportionately afraid of it than they should be. There's this whole idea of misfearing, which is fearing the wrong thing....Women's misfearings. Women ought to be really afraid of heart disease, right? That's what they should be afraid of, that's what's probably going to kill them. But they're super afraid of breast cancer because we've made everybody so damned aware of it with the pink ribbon first of all, and secondly because we've created this whole new class of survivors through mammography, the so-called survivors. So there's a lot of women who have had it all over the place all of a sudden, so it's much more seemingly prevalent, and there was an authentic rise of course of breast cancer in the '70s and '80s and '90s..."—Peggy Orenstein, Media, NYTimes

APPENDIX H. Sources of Heterogeneity across Different Diseases

Risk Perception	*"There tends to be an agreement of the community that PSA screening may not work. In the public health scene there is equally an agreement that even so there might be some problems, with mammography in general it's more beneficial than harmful to women. So the perception of the two screening processes is different."* —Peter Juni. MD-PhD, Director, Applied Health Research Centre, St. Michael's Hospital, and Professor of Medicine, University of Toronto
	"I know less about PSA screening. My impression is that the evidence of the benefit of PSA screening is less than for mammography, but with mammography, which I have studied a bit more, I think the-- it's clear that there are risks associated with just broadly advocating mammography." — Media, Science Reporter
Understanding of benefits and harms	*"It's a little bit easier to demonstrate the over treatment for PSA than it is for mammography, but it's interesting, and for years, I think, we were telling our patients, or at least I was telling my patients, oh, the PSA is a really limited test. We really need to be careful about how we use this. The benefits are very small and the harms are significant...It's only been in the last few years that I think many of us have realized that mammography as a test itself is not that different from the PSA. It's a little bit harder to see the over diagnosis, which I think is one of the problems. With prostate cancer, we just know that there's so many low-grade prostate cancers that don't progress. There's probably, you know, there's also lots of breast cancers, but we just can't tell."*
	"...I think most women don't, and they don't understand it, and I think this is one of the things I try to explain with them when I talk to them, is that, you know, many people are going to be-- about 19% of people who are diagnosed with cancer over a ten-year period are overdiagnosed, and they're going to be treated for a cancer, get surgery and radiation and maybe chemotherapy for a cancer that would have never caused them problems. And people sort of get that. I think they get it better with prostate cancer, with this idea that, you know, you're going to have your prostate removed or have surgery and be left with a high likelihood of erectile dysfunction, and a moderate likelihood of urinary problems, and all kinds of surgery complications. I think those people, I think it's a little bit easier to get their head around that, for prostate cancer, because the side-effects are so long lasting. I think women think a little bit differently about what it means to have their breast removed, but, you know, I think that overdiagnosis is increasingly understood by women, and I actually think that back when the USPTF made their recommendations, one of the biggest issues was that, when they were talking a lot about the benefits and the harms, they really focused on the harms of false positives and unnecessary biopsies, and I think women are more likely to say, you know, "I can handle a false positive. Even if it's scary, I can get over that, but I can't get over death." So they were trying to weigh this balance between false positives and the benefits, and they really should have said more about the overdiagnosis issues..."—Nancy Keating, MD, PhD, Division of General Internal Medicine, Brigham and Women's Hospital, Department of Health Care Policy, Harvard Medical School
Treatment Options, Harm Reduction Technology	*"On the other hand we have very good therapeutic possibilities nowadays, that mean, that therapeutic window has become much larger than at the beginning of the '90...This was not the case in the '90s...this wide therapeutic window with breast cancer is important here. Again this contrasts with the narrow or the more narrow window that we have for colon cancer. You see, it is a very good idea to get colon cancer detected*

	before it actually becomes a cancer, that's the polyps of course... But if not that then second best, to get it while it hasn't metastasized yet. So the situations are really, really different....In prostate cancer you see again the same reflected in a way. You see on one hand that indeed typically there aren't organized screening programs, systematic screening programs recommended [in Europe], because people are in agreement or tend to be in agreement, many of us of the public health community, that it may be problematic as well." —Peter Juni. MD-PhD, Director, Applied Health Research Centre, St. Michael's Hospital, and Professor of Medicine, University of Toronto
	"I think probably the risks of PSA screening can outweigh the benefits, because the procedures that are done for prostate cancer has much more morbidity associated with them than a breast biopsy. They can cause urinary incontinence and they can have sexual dysfunctions, having surgery for prostate cancer. I think it's gotten better, there's less of that, but men really need to aware that they might be left with some permanent problems for a cancer that may not have killed them."—Shelley Justa, MD, Family Practitioner
Industry Opportuniti es	*"In the case of prostate cancer you do a PSA test, leads to a biopsy, leads to treatment, leads to follow up. If you're impotent then you want to try Viagra, Cialis, Levitra, all sorts of erectile, to correct that. If you're incontinent and you can't control your flow the urine, then you have an artificial sphincter and all sorts of things. So the amount of money that you can make from an inexpensive PSA test down the road, I think far exceeds what you can make with a colonoscopy."* —Richard Ablin, University of Arizona, College of Medicine, Professor of Pathology

APPENDIX I. Sources of Heterogeneity across Countries

Risk Perception, Industry	*"I think the major determinants are, I think, the commerce and industry and the perception of the public. That's not the case in Europe. I think in the US, I think these are, let's say, quite important. I believe in evidence. This is my major role and my major career, but I certainly believe in evidence. I think in many instances it is number one, certainly evidence-based, doing trials, doing quantification, and cost-effective itself, so it should be number one, but because you especially asked about how much screening is going on, and I think in the US, I think these public perceptions and industry are forcing it to do play a major role, I think, yes."* —Harry de Koning, Professor of Evaluation of Screening, CISNET comparative modeling group
Healthcare System	*"I think basically the more defensive health care system in the US compared to Europe in general terms, so, again, with all the legislation and all the law suits, etc, etc, it's much more difficult to mean something in the US than it is in Europe, and the rest is fee. There's the fee for, what is it? Yeah, fee for service, which in many European countries is certainly not the case, or at least much less, so there is at least not such an important role, whether you do a PSA test at age 80 or not. It doesn't matter much for the health care doctor in Europe. So those are, unfortunately, I think a couple of important things..."*
	"...I think many doctors just have individual thoughts and ideas about that, and that plays a role, and that is why I think national programs like in the European countries where people are just invited independent of the physicians, it's very helpful in the sense

	that it gives you the correct information, and you can decide on your own. That's how in many European countries it's being done..." *"...I think in many cases, it is indeed the physician not following the guidelines, and the system, it's a totally different system in the US, because, compared to Europe for instance, makes it easier not to follow guidelines in the US than it is in Europe. So, indeed, to some extent we circumvent the physician in the guidelines and send out invitations to everyone..."* *"...Because anyone can knock on your door of the physician and ask for a test and pay for it. So it's a sort of open entrance system, I think [in the US], in many instances, and that's not the case here, so as an example, in the Netherlands, people are insured, and you cannot go directly to a hospital. You have to go through your GP to your physician, to your sort of primary care system, and that primary care system is, well, it's sort of with, let's say, rational people, not all, but anyway-- it's sort of a border, a cutoff, there's a first sensible note, in the Netherlands and, I think, in many more countries in the Netherlands, that can just explain to the individual and say, "I think you should not go for the PSA testing," and that helps. And I'm not sure how much that is being done in the US." —Harry de Koning, Professor of Evaluation of Screening, CISNET*
Liability	*"I think the most important one is that most of your [indiscernible 00:24:30] are not driven as much as you are regarding liabilities, liability cases, to end up in court for having missed a breast cancer. This makes a big difference if it comes to overdiagnosis. So the problem of over diagnosis is not as pronounced in Europe, I would assume it has data for that to support it or the observational data of course. It's not as pronounced in Europe as it is in the U.S. In the U.S. it's to an extent which is really quite scary. It is still too high here, but that it makes quite a difference." —Peter Juni, MD-PhD, Director, Applied Health Research Centre, St. Michael's Hospital, and Professor of Medicine, University of Toronto.*
Evaluation of Evidence	*"I think it should be peer quantification of the harms and the benefits, and from authoritative panels. I'm not sure if the US taskforce is that for the US. I think probably yes. There's politics involved, but I think nevertheless, I think we here in Europe really believe in authoritative panels that are independent as possible and weigh the evidence that gets presented by the experts. I think that should be the situation. That should be the ideal situation." —Harry de Koning, Professor of Evaluation of Screening, CISNET comparative modeling group* *"So the evidence or coming to the recommendations, which is something else than the evidence, I think, unfortunately. I would say that definitely it differs, for the US, for Europe. For example, in Norway, we are recommending mammography screening every other year to women 50 to 69 years old, and we do not recommend PSA screening. Actually, I think-- I don't think they're recommending against it, I think it's more like you do not recommend it. So in the US, of course, there are differences." —Clinician, Academic*
Biopsy Referral Rate, Disease Threshold	*"You know the studies have shown women can have an up to 50% risk of at least one possible false positive after ten years of screening, and that's humungous. So I think that's a big risk that it also comes with a huge risk of a biopsy, or something you would never have needed...And in the US we have a much higher recall rate than in Canada or Europe, and obviously that's a tradeoff. They have a lower threshold for just calling a mammogram positive." —Natasha Stout, Professor, Harvard Medical School*

	"So what prevents me from doing more biopsies? What prevents me from doing extra tests? Every extra test makes me make money. So there is this conflict of interest for the doctors. There is this huge financial incentive if you do extra tests, and definitely the extra incentive is if you miss it, that's it. That's the case with every disease in the US. That's why in the US, there is this article that compares biopsy rates in the US and UK. We have twice as many biopsies as compared to the UK in the US."—Oguzhan Alagoz, Professor, Industrial and Systems Engineering, University of Wisconsin-Madison, Cancer Intervention and Surveillance Modeling Network (CISNET)
Effect of Media and Information Load on Laypeople	*"So, for instance, I think that [inaudible 20:22] about breast cancer screening in the world every now and then is, of course, really confusing to women. Also in Europe, again, fortunately, many people still come, and the attendance rate doesn't drop too much, but it is really an issue that, indeed, conflicting data now come into the press, and many of the laypeople do not know what to do with it, and, of course, to write it will also lead to confusion in physicians, and from the care people, and that is maybe a reason why an individual with a certain idea already in his head, or her head, with the confusion, it doesn't help them. It doesn't make-- it doesn't help to say, there is one guideline and it helps me out now. So I agree with that, yeah."—Harry de Koning, Professor of Evaluation of Screening, CISNET comparative modeling group*
Timing of Screening	*"In every country that has begun population screening there has been a tipping point at which the mortality starts to decline, related to when they started screening. For instance, in the U.K. they started screening early. In Germany they started screening later. In the Netherlands they started screening a little later. In the U.S. they started screening in the '80s, and our tipping point was 1990. In England the tipping point was about 1985. In Germany the tipping point was about 1995. Every state that started population screening has seen a decline in mortality. It can't be because of drugs, because they were getting drugs beforehand"—Blake Cady, MD-PhD Emeritus, Surgeon Oncologist, former member or American Cancer Society (ACS) tumor board*
Enthusiasm for Screening	*"A lot of this has to do with the way we have convinced people over the years that cancer screening is so important, and we have, I really do believe, as a community, we've been overselling the benefits, and underselling the harms, and I think that there's lots of enthusiasm for cancer screening in America, and we've trained people to think this is what we need to do, and when we start telling people don't do it, they feel like something's being taken away from them I think... and I think that we haven't done a very good job of communicating that...."—Nancy Keating, MD, MPH, Professor of Health Care Policy at Harvard Medical School and an Associate Physician at Brigham and Women's Hospital*
Stigma	*"The second aspect is there is quite a bit of variation. So I think the extent of stigma U.S. patients, if it comes to mammography, experience when they don't undergo mammography, this extent of stigma is not happening in Switzerland. There will also be some, but it's not as pronounced. But it may as well happen to an equal extent, for instance in Italy, what I heard anecdotally, what's the word, anecdote?"—Peter Juni, MD-PhD, Director, Applied Health Research Centre, St. Michael's Hospital, and Professor of Medicine, University of Toronto.*
	"I haven't studied PSA screening as much, but I know there's a lot of people that I've spoken to, doctors consider it to be really misused. In this country, in the US, it's much more used than elsewhere, other countries...I think, yes, PSA testing is overused, but I think there too people are becoming more sophisticated about it, and

APPENDIX J. Sources of Heterogeneity Over Time

Incidence Trends	*"The incidence of breast cancer basically doubled at the time of the introduction of mammography and about 10-15 years later annual mortality from breast cancer started to drop about 1-1.5% per year. The steady decline of breast cancer mortality (over the past 25 years breast cancer death has dropped by 30%) is most likely due to both, early detection by mammographic screening and improvement in the efficacy of therapies for early stage breast cancer."* *—Lajos Pusztai, Yale School of Medicine, Chief of Breast Medical Oncology, Co-Director of the Yale Cancer Center Genetics and Genomics Program*
Treatment Rates	*"The big thing that's really increasing in frequency is bilateral mastectomy. So people are getting diagnosed with breast cancer, particularly younger women, and even though there's no evidence that bilateral-- so you take off the effected breast, and you take off the unaffected breast, so it's sort of like a prophylactic surgery. Even though there's no evidence that that saves lives, women are increasingly choosing it, at high rates, particularly younger women.... particularly amount younger women who don't want the potential of having another breast cancer, because the anxiety for women of going through breast cancer, even when, you know, 90% of breast cancers are early-stage and curable, and there's no evidence it's going to change their life expectancy, and they seem to get that, they still want to have the other breast removed. Some of that has to do with surgical options, because if you want to have reconstruction, many of the plastic surgeons will encourage women to have both out, because they think they can get a better cosmetic outcome if they do both breasts at the same time."—Nancy Keating, MD, PhD, Division of General Internal Medicine, Brigham and Women's Hospital, Department of Health Care Policy, Harvard Medical School*
Technology	*"There's a thing called the Will Rogers effect. Do you know the Will Rogers effect? Will Rogers was a famous American humorist in the 1930s and he said during the Dust Bowl, during the drought in the 30s when the people from Oklahoma called the Okies moved to California, the IQ of both states went up. Dr. Blake: It was a humorous thing, but it's a profoundly important concept in cancer because the more sophisticated your diagnostic study, the more positive results you get. ..." Interviewer: More technology finds more cancer. Dr. Blake: That's right. So when you go from 1 slice through a node to 15 slices you increase the number of positive nodes, but what are those things that you find? Are they bigger?..."—Professor Blake Cady, MD-PhD Emeritus, Surgeon Oncologist, former member or American Cancer Society (ACS) tumor board* *"If you go back to the '70s when screening first started, first of all, before that time most cancers were just detected on self-exam and were larger...and the only treatment then was mastectomy. Then moving into the '70s and '80s, we're picking up smaller cancers on mammography, and the studies were done in showing that the survival is equivalent whether you do a mastectomy or a lumpectomy followed by radiation... So it's kind of the technology and the science have, the science of the surgical treatment or the treatment of breast cancer, I think have evolved in step. As we're detecting smaller and smaller cancers, at the same time we're saying, "We've already proven*

	that more surgery is not better. So how much is absolutely necessary?" —Deanne Attai, Former President at American Society of Breast Surgeons, Clinical Professor of Surgery UCLA
Treatment Efficiency	*"There's another important thing to consider when thinking about survival improvement from screening and early detection. The premise of screening is that earlier detection of cancer leads to greater cure rates because our therapies are more effective for earlier stage cancer. As the efficacy of treatments for later stage (stage II-III) breast cancers improves the survival benefit from early detection could decrease. For example, in the early 1980's survival for a 3 cm node negative breast cancer could be as low as 75% (due to limited postoperative treatment options), today survival is likely to be over 85%. To make a thought experiment, let's assume that in the near future, with new treatments, survival of all 3 cm or greater breast cancers improves to over 95%. At that point the survival benefit from mammographic screening (i.e. detecting cancers that are subclinical and are 1-2 cm large) will be very small because both the small and larger cancers can be cured at diagnosis. However, screening still could have benefits in terms of allowing less toxic therapies for earlier stage cancers rather than allowing the cancer to grow to a clinically detectable larger size when treatment would be more intense and therefore more costly and more toxic."* —Lajos Pusztai, Yale School of Medicine, Chief of Breast Medical Oncology, Co-Director of the Yale Cancer Center Genetics and Genomics Program

APPENDIX J. Elements of Perceived Harms and Benefits Environment

Academic	*"The most important harms are really over-diagnosis and over-treatment. Those are basically the most important ones. To get a good schedule on that is crucial."* —Harry de Koning, Professor of Evaluation of Screening, CISNET
	"I think most women don't, and they don't understand it, and I think this is one of the things I try to explain with them when I talk to them, is that, you know, many people are going to be-- about 19% of people who are diagnosed with cancer over a ten-year period are overdiagnosed, and they're going to be treated for a cancer, get surgery and radiation and maybe chemotherapy for a cancer that would have never caused them problems. And people sort of get that. I think they get it better with prostate cancer, with this idea that, you know, you're going to have your prostate removed or have surgery and be left with a high likelihood of erectile dysfunction, and a moderate likelihood of urinary problems, and all kinds of surgery complications. I think those people, I think it's a little bit easier to get their head around that, for prostate cancer, because the side-effects are so long lasting. I think women think a little bit differently about what it means to have their breast removed, but, you know, I think that overdiagnosis is increasingly understood by women, and I actually think that back when the USPTF made their recommendations, one of the biggest issues was that, when they were talking a lot about the benefits and the harms, they really focused on the harms of false positives and unnecessary biopsies, and I think women are more likely to say, you know, "I can handle a false positive. Even if it's scary, I can get over that, but I can't get over death." So they were trying to weigh this balance between false positives and the benefits, and they really should have said more about the overdiagnosis issues..." —Nancy Keating, MD, PhD, Division of General Internal

	Medicine, Brigham and Women's Hospital, Department of Health Care Policy, Harvard Medical School
	"There is anxiety to reading off a mammogram. A lot of false positives. It's almost seven, eight percent on each mammogram, and if you take ten mammograms that means there is a ten percent chance that the woman would get their false positive. And false positives are bad, because the moment you tell her that it's abnormal, she thinks, "I have cancer." So that's why that's a huge harm..." —Academic, Clinician
	"So what happens is, millions and millions of men were over diagnosed and over treated. So you have thousands and thousands of men going around that are incontinent, that are impotent, and that have the psychological effects of these situations. The doctors, the urologists, in some cases they're not very kind. A man would come and say, "I have prostate cancer," the doctor would treat him, and the man would say, "Will I be impotent? Will I be able to have an erection and have sex?" the doctor will say to him, "There's no sex in heaven." Meaning that if I remove your cancer you don't have to worry, because if you go to heaven and you don't have your prostate and you're impotent, there's no sex in heaven. So they would say, "There's no sex in heaven, and if we have a problem, if you're impotent, we can fix it. We can fix it medically with Viagra, Cialis, Levitra. We can put in a pump, we have various ways for erectile dysfunction." — Richard Ablin, University of Arizona, College of Medicine, Professor of Pathology
Clinician	*"I think the benefit, at least in my mind, is to be able to catch a breast cancer at a time that's so early that chemotherapy could be skipped. In my mind, finding these small breast cancers, I interpret that as a success because then I can spare them chemotherapy if I can. That's really the benefit. I would say the risk are those of false positives, obviously it's very stressful for a woman to get screening, and there's a little spot, and then you got to come back and get a biopsy, and when everything is said and done it was all a scare for nothing. Obviously that's healthcare dollars being spent, at the end of the day not making that person healthier." —Erin Hofstatter, School of Medicine, Assistant Professor of Medicine (Medical Oncology) and Co-Director, Genetic Counseling Program*
	"Prostrate, it's very unclear. I think probably the risks of PSA screening can outweigh the benefits, because the procedures that are done for prostate cancer has much more morbidity associated with them than a breast biopsy. They can cause urinary incontinence and they can have sexual dysfunctions, having surgery for prostate cancer. I think it's gotten better, there's less of that, but men really need to aware that they might be left with some permanent problems for a cancer that may not have killed them." —Shelley Justa, MD, Family Practitioner
	"If prostate cancer's just in the prostate, they could do surgery, prostatectomy. But again once it's spread to wherever, let's say bones, a lot of times they don't do surgery they only do radiation of the prostate and then they try to treat the metastatic disease with hormonal manipulation or chemotherapy. So very different whether or not they resect the primary tumor, or whether or not they try to just get the patient through living with the tumor..." —Clinician
	"If you have breast cancer you want to get the best treatment, which is most likely to cure you. Currently the chance of cure is closely linked to the size of the cancer at presentation. For example, less than 2 cm breast cancers, without spread to the lymph

	nodes, have cure rates over 90%, on the other hand cancers that are 5 cm or larger or have multiple lymph nodes affected can have cure rates below 50% .." Which group you would like to be? Obviously, if you can do something about it, you want to have the smallest possible cancer. This is where mammographic screening can help. The down side, we increasingly recognize that some mammographicly identified cancers are cancers in name, and appearance, only. They would not harm or shorten the life of a person even if left untreated. This is called over-diagnosis. The extent of over-diagnosis, that is what faction of cancers picked up by mammogram would have not harm an individual, is intensely debated." —Lajos Pusztai, Yale School of Medicine, Chief of Breast Medical Oncology, Co-Director of the Yale Cancer Center Genetics and Genomics Program
Policy	*"The potential benefit is finding a cancer that may harm the patient within his remaining lifetime. The disadvantage is what we call PSA anxiety, in other words concern on the part of the patient about having an undetected cancer in spite of a normal finding. The others are the risks of biopsy, which are sepsis, urinary tract infection without sepsis, bleeding, urinary retention... Interviewer: Are these common after biopsy or are they considered to be rare cases? John: They're unusual, I would say probably the nature of 4%, maybe 5%" —John D. Barry, Professor of Urology and a Professor of Surgery, Oregon Health and Science University, former chair or AUA*

"[Benefits are] Saving lives, improving quality of life. Interviewer: Harms of screening? Matt: Potential harms? Well you have the harms of screening itself, so the screening test may be expensive or painful or difficult, and then you have the follow up of the false positives which may be expensive, difficult, painful, and anxiety producing. So that's all about the test. Now once you have a positive test, a positive screen, you still may have harms because of the treatment. In a screening paradigm, if there's 100% adherence everyone who gets a positive screen, maybe then gets a diagnostic test and then treated, that process can have harms. /..So there are harms of the screening process and then there are harms that accrue the people who are positives. Now if they are false positives they can only get harm, they can't get benefit. If they are true positives they can get benefit but they can also get harm."— Matt Gillman, M.D., S.M. Director, Environmental Influences on Child Health Outcomes (ECHO); Office of the Director, National Institutes of Health

"In every country that has begun population screening there has been a tipping point at which the mortality starts to decline, related to when they started screening. For instance, in the U.K. they started screening early. In Germany they started screening later. In the Netherlands they started screening a little later. In the U.S. they started screening in the '80s, and our tipping point was 1990. In England the tipping point was about 1985. In Germany the tipping point was about 1995. Every state that started population screening has seen a decline in mortality. It can't be because of drugs, because they were getting drugs beforehand. Here is the Norwegian study in which they claimed that screening was of no value, and yet despite that if you read the article closely, one third of the total reduction of breast cancer mortality in Norway, they admitted, was due to screening." —Clinician, Policy Maker |
| **Advocacy** | *"I hear a lot said about false positives and that they don't want to screen women because of false positives, and that for every, I think, 1900 women screened there will be 5 that are identified, one of which will ultimately be a breast cancer and 4 which will either get additional screening or biopsy, some people would say unnecessarily. But all the women that I speak to and I say that to say they would much rather go* |

	through a little anxiety, because that's the big excuse given I think, is that, "We don't want to cause these women undue anxiety." But I think women will tell you that they'd rather go through a little bit of anxiety and a biopsy or additional pictures, through mammogram or ultrasound or MRI, than go undetected. Because mortality's higher at late stage, and that's a fact." —Patient Advocate *"I personally believe that for average risk women, women without elevated risk, that there is reason to question whether we should go looking in healthy women for early signs of breast cancer. I believe the data shows that the lead time that mammography gives you does not change the outcome, and that instead a whole bunch of women are harmed because they are treated for nonlethal cancers, their body, psyche, minds are treated for nonlethal cancers. A whole bunch of women are scared and scarred because of the biopsy and the fear around false positives..."—Patient Advocate* *"...that focused on sleepless nights. How do we reduce sleepless nights, how do we reduce the waiting time that patients...This was particularly in their breast clinic, as I recall, it was actually a cocktail conversation so I haven't done any reading on it. But how do we account for that, and how do we hold ourselves as a medical institution accountable to these women in that vein. Ozge: So these number of sleepless nights, were they meant to be a proxy variable for anxiety? Interviewee: Yes. I think for anxiety as well as straight up sleeplessness, which in and of itself is a risk factor in all kinds of things. But yes, the goal was to measure and evaluate how long patients were waiting without knowing." —Patient advocate*
Media/ Science Reporter	*"I think the benefits are pretty clear. The harms can be subtle, some people think, this business about needless anxiety for many people who don't need to have it, but also, you know, causes untold-- I've talked to surgeons. A lot of women get mastectomies who don't need them, so it does-- it seems like a harm to me, and being related to the anxiety. Then they feel they can be less anxious because they've done this. Of course, any time you do a medical procedure, there's a risk of something happening to you. Being in the hospital is dangerous." --—Media, Science Reporter* *"There's psychological consequences. You can say that's not bad, but it does. If you get a diagnosis that you've got a tumor in the breast, that's going to change your outlook on things, raise anxiety. And then most of the biopsies are pretty straightforward and simple, but sometimes the biopsy doesn't answer all the questions, and you have to do more surgery and more testing. So most of these women, as you know, who have a-- we were talking about ductile carcinoma, most of them would never develop a real cancer, a threatening breast cancer. So, yeah, there are harms. It's really hard to calculate this question, whether it's worth the harm, because any individual you ask will say, "I don't mind the hazard if it saves me from getting cancer." In the individual case, you could say, yeah, it's always worth it to get screening if it finds cancer. If it finds the cancer. But when you look at it as a public policy, you're forcing a lot of people to get biopsies that really don't need them, and it's really difficult, I think, for me, to judge whether it's worth it or not worth it, but it's a new technology that's causing a lot of medical work and expense and anxiety that, when we look at the broad picture, we can see it's really not improving health. Anyway, so that's-- there are two different perspectives: The individual one, and then the sort of public health one, and quite often you will hear people say, "Screening saved my life, so it's worth it for everyone..." —Media, Science Reporter*

	"I think from-- I mean, again, I don't have the data on this, but I think that from speaking to women themselves, I think that, yes, when you talk about the drawbacks and benefits of screenings, women are much more afraid of a cancer that is undiagnosed than having a screening and having the biopsy. You know, I'd rather have that knowledge and have that control than, you know, be thinking about cancers that I'm not doing. And once I do wind up with a cancer, and its not-- and I could have caught it earlier. So, yeah, and it's the same thing, when they choose to have a mastectomy versus a lumpectomy, that many of them don't want the anxiety of having to go back for all these screenings and having to worry. They'd rather just know they did everything they could to get rid of every breast cell they have in their body as much as they could." —Deborah Kotz, FDA Reporter
Patient	*"I think that mammography is not without risks and we treat it as if it is. The risks are obviously a small risk of radiation exposure, but that is cumulative over time and the sooner that starts the more you accumulate. But I also think the entire area of overtreatment is critical and I think our feelings about it are spurned by a gut reaction to get the cancer out. I think the issue of overtreatment is a much bigger issue than we give it credit for. I understand viscerally and I understand as an early stage patient that desire to cut as much as necessary to make it go away. I'm the perfect example of how that doesn't work." —Patient, Patient advocate*
	"I was like, "What are you talking about? The life that was saved was mine. I am the woman whose life was saved by that under 50 mammogram and you need to know who I am," so that was why I wrote my first article. Also because of the particular complications of being a 35 year old with cancer, I hadn't had children and I wanted to have children, and what was this going to mean. So there was a particular story that I thought I had to tell at that point and I wrote a cover story for the New York Times Sunday Magazine at that point, that was called '35 and Mortal' I think. It was like the diary of a young woman with breast cancer. When I look back on that story now, it has pretty much everything in it that now bugs the crap out of me about stories about breast cancer." —Peggy Orenstein, NYtimes

APPENDIX K. Broad Boundary Feedbacks around the Screening Decision

Some participants emphasized the effect of fee for service and that self-referral increases PSA screening, the fact that Medicare pays for all FDA approved treatments, and that doctors usually are paid consultants of companies, suggesting a symbiotic relationship between medical-industry and conflict of interests.

Academic	*"In the case of prostate cancer you do a PSA test, leads to a biopsy, leads to treatment, leads to follow up. If you're impotent then you want to try Viagra, Cialis, Levitra, all sorts of erectile, to correct that. If you're incontinent and you can't control your flow the urine, then you have an artificial sphincter and all sorts of things. So the amount of money that you can make from an inexpensive PSA test down the road, I think far exceeds what you can make with a colonoscopy." — Richard Ablin, University of Arizona, College of Medicine, Professor of Pathology*

	"We interviewed several people, and one of the persons in fact that we interviewed, his name was Jules Harris. He was actually one of the advisors at the [FDA's 1994] committee. The test got approved, now what happened is when the first test was approved in 1986, the only way that people had to detect prostate cancer at the time was either by a digital rectal exam or a biopsy. When the test became approved in 1986 people went crazy, they went out of their minds because they said, "Here we have a noninvasive test, we have a blood test." Even though the FDA in '86 only approved this for monitoring, the pharmaceutical biotech industry and doctors, urologists, they started to use this test off label to detect cancer. Using it off label as they used it, it's criminal. So for eight years from 1986 until 1994, they used this test to detect prostate cancer.....What happened is that they started, they meaning the urologists, general practitioners, everybody started to use this test to detect prostate cancer. The way they did it was they spread the word that prostate cancer was increasing, the incidence was increasing. The reason why the incidence was increasing, because they were using the test. So the whole idea was here, that with fear, you scared, you told patients, "You have to have a PSA test because prostate cancer will kill you. If you have a PSA test we can detect the disease early enough so we can treat it and we can cure it." So that was the driving force, was fear. The fear drove the patients to get the test." —Richard Ablin, University of Arizona, College of Medicine, Professor of Pathology
Clinician	*"A friend of mine just told me, she had told her doctor, "I'm doing mammograms every three years," that's what she decided. Her doctor said, "Okay," and she gets phone calls from the HMO saying, "You haven't done your mammogram. Why haven't you done your mammogram? Make your appointment for your mammogram," annually. So there's a lot of pressure also, the medical establishment, your insurance company, whatever, your doctor, your HMO is going to press you to do it every year starting at 40. So that's the other piece." —Clinician*
Advocacy/ Activist Group	*"One of the things I hope we end up talking about is the role of corporate marketing teams. When we look at all the places where women are getting information about mammography and screening, we must acknowledge the role of corporate marketing teams. Let's see, you've got nonprofits, we talked about that. You've got industry groups, the various medical groups. You have the USPSTF. I think an important player that we need to talk about is corporations and corporate marketing teams... They make money by selling products which they claim demonstrate how much they care about cancer. To sell a product, you need to sell a story. And the easiest way to do that is to provide a simple narrative, which is presented as uncontroversial and nothing but beneficial. Promote early detection and screening programs, is part and parcel of pink ribbon promotions in the U.S." —Karuna Jaggar, Executive Director, Breast Cancer Action*

"I think you could do a nice 'follow the money'. We call it the cancer industry, which is a way of highlighting the ways in which the different parts or pieces reinforce each other. When the same companies that sell breast cancer treatments, donate to programs which drive up the number of women diagnosed with the disease, there is a direct benefit to those corporations. Because we currently lack the tools to determine which breast cancers will be fatal, virtually every woman diagnosed with breast cancer will have surgery, and most will also have radiation, tens if not hundreds of thousands of dollars of medications, and possibly plastic surgery." — Karuna Jaggar, Executive Director, Breast Cancer Action |

Media/Science Reporter	*"Because you've got members of congress who has their constituents who are very pro-screening, and feel that worry that the government is going to take that away from them for health care costs. So it's an interesting piece that you're doing, because it's not just a matter of looking at the evidence and saying it's appropriate or not..."* —*Deborah Kotz, FDA Reporter*

APPPENDIX L. Effect of Media and Advocacy Groups

Academic	*"Media and advocacy groups I think are doing a terrible job.... For example, when taskforce said, "Don't do screening before age 50" they highlight all these stories from individuals who were saved from cancers, and for me that is really misleading...they like this whole sensational, cool sort of sexy story, I don't think that they are doing a good job. And I think advocacy groups, I think are similar. Actually-- advocacy groups are like, "Screen screen screen." There is this understanding... but that doesn't mean that more screening will always save it. Okay, let's screen everyone, every month."*— *Oguzhan Alagoz, Professor, Industrial and Systems Engineering, University of Wisconsin-Madison, Cancer Intervention and Surveillance Modeling Network (CISNET)*
Clinician, Policy	*"Advocacy groups can be good. The American Cancer Society has a program that's in place. Our own institution has patient advocacy groups that are usually cancer specific, and they meet and talk before and after treatment. There's not much discussion about screening. Most of the discussion is about treatment, treatment morbidity, survival, and healthcare cost".* *"The role of media is important because number one, they can create a problem. Then number two, they or their advertisers or board of directors can propose a solution that results in profit, I guess. So those are concerns about the media, sometimes it's good, sometimes it's bad. It's good in the sense that it makes patients aware, it's bad if it frightens them. But fear, again, is on the part of the individual who gets the information.* —*John Barry, Professor of Urology and a Professor of Surgery, Oregon Health and Science University, Former President AUA* *"I think that the media and the celebrity effect, as I've written about, is a bit of a problem. It's a bit of a problem because women then get the sense that it's no big deal, you just go have your breasts removed and then you're back doing your normal thing, and it's no big deal. Nobody sees Angelina Jolie on the first day after surgery when she's in pain and has drainage tubes and all that sort of thing."*— *Deanne Attai, Former President at American Society of Breast Surgeons, Clinical Professor of Surgery UCLA*
Advocacy/ Activist Group	*"I think positively, they impact for screening. I think sometimes people will get bad information about new treatments and research, because you hear on the nightly news that a possible cure for breast cancer...I don't know, I always think they kind of sensationalize research findings so that people think it's that silver bullet they want. But in terms of getting screened and spreading the word, I think they [media] have a very positive effect on that."* —*Patient Advocate* *"I do think that the media goes to the so-called experts, and the experts are the big organizations, the big organizations have conflict of interest. So when the media looks to experts they look to the ACS and Komen, and they do not discuss the conflict of*

	interest. So the media upholds these expert opinions without questioning the opinions, so that's one thing. The media is notoriously bad at medical data. The media is always looking for catchy catchphrases, that they drum up fear, the media's business is drumming up fear and then offering simplistic solutions…"—Patient Advocate *"As far as advocacy groups, it sort of depends on the group. I think many of them are very good at just promoting good information. So some advocacy groups I think do a very good job. I think most of them do, honestly. The BRCA groups I think do a very good job in educating patients about prophylactic mastectomy. Obviously that's a completely different population because they're at such high risk."* *"There's a multitude of issues that come into play for advocates. So it's been important to stay up to date on that, as well as any number of other breast cancer specific topics. Right now I am serving as …and we are the only nonprofit that we know of that goes through a peer reviewed grant process." —Patient advocate*
Media/ Science Reporter	*"I don't 'mean to sound arrogant by saying that, but in general I feel like the media has not been very on top of this issue. They have not been leaders, they have not reported well, they have bought into a lot of myths. —Peggy Orenstein, NYTimes* *"Initially, I think, we were all kind of participating in the same thing, which is to say promoting the value of screening. And it always happens with the media, I think. A new technology comes in and then everybody says, "Wow." And the media will of course reflect that. So it's a fascination with new technology, and hope that it will be sort of a fix. So I think the media definitely participated in that. I don't think the media has given enough attention to the hazards, the bad side of screening. I don't know how to evaluate that, but I think there are more critical articles now, but it's not in the same degree as we supported screening in the beginning. Advocacy groups, likewise, I think that they have-- some of them are quite sophisticated about the risks of screening. I've tried to get research on that, but they don't-- I don't think they want to tell their members that they shouldn't do something like that. I think it's just not part of being an advocate".* *"And I think the media tend to look on the advocacy groups favorably. And there are some areas of medicine where the advocacy groups are quite closely tied in with industry groups. I don't know if that's the case in, say, some of these breast cancer advocacy organizations…"* —Media, Science Reporter
Patient	*"So I don't remember which specific foundation I've heard the name of but I think we grow up in the U.S. hearing about these things a lot. Even in schools they put up all these pictures in the bathrooms saying, "This is how you test for yourself," like self-examine, and there's always a foundation name." I don't actually participate in any of this, and I don't know about specific foundations. So we didn't really think too much about like, "Oh this place doesn't…," like when we were making decisions about hospitals or like when the other place said, "You need to pay $2000," we didn't really mind too much because my sister and my mom both knew, "There are so many foundations out there, that we will be covered eventually even if we have issues," we kind of knew that… We knew U.S. has terrible health insurance system, but in terms of breast cancer there are so many foundations where we can get help from, and we kind of knew that. Then the hospitals also give out a lot of pamphlets and things like that about foundations."*

APPENDIX M. Perceived Sources of Biases

Category of Disagreement	Pro	Con
Media and advocacy influence	*"I think positively, they impact for screening. I think sometimes people will get bad information about new treatments and research, because you hear on the nightly news that a possible cure for breast cancer...I don't know, I always think they kind of sensationalize research findings so that people think it's that silver bullet they want. But in terms of getting screened and spreading the word, I think they have a very positive effect on that."* —Patient Advocate *"Advocacy groups can be good. The American Cancer Society has a program that's in place. Our own institution has patient advocacy groups that are usually cancer specific, and they meet and talk before and after treatment. There's not much discussion about screening. Most of the discussion is about treatment, treatment morbidity, survival, and healthcare cost."* —John Barry, Professor of Urology and a Professor of Surgery, Oregon Health and Science University	*"Media and advocacy groups I think are doing a terrible job.... For example, when taskforce said, "Don't do screening after age 60," they highlight all these stories from individuals who were saved from cancers, and for me that is really misleading...they like this whole sensational, cool sort of sexy story, I don't think that they are doing a good job. And I think advocacy groups, I think are similar. Actually-- advocacy groups are like, "Screen screen screen." There is this understanding... but that doesn't mean that more screening will always save it. Okay, let's screen everyone, every month."* —Oguzhan Alagoz, Professor, Industrial and Systems Engineering, University of Wisconsin-Madison, CISNET *"Initially, I think, we were all kind of participating in the same thing, which is to say promoting the value of screening. And it always happens with the media, I think. A new technology comes in and then everybody says, "Wow." And the media will of course reflect that. So it's a fascination with new technology, and hope that it will be sort of a fix. So I think the media definitely participated in that. I don't think the media has given enough attention to the hazards, the bad side of screening. I don't know how to evaluate that, but I think there are more critical articles now, but it's not in the same degree as we supported screening in the beginning. Advocacy groups, likewise, I think that they have-- some of them are quite*

		sophisticated about the risks of screening. I've tried to get research on that, but they don't-- I don't think they want to tell their members that they shouldn't do something like that. I think it's just not part of being an advocate." —Media, Science Reporter
Cost Containment	Cost containment as a bias is mentioned by some interviewees directly or indirectly. Some responses to this argument include: *"If you start calling it a cost thing, then people start getting really suspicious on what your motives are. So I think there's enough evidence on the harms of that we should just be trying to communicate what the true benefits and harms are, and help people understand that. And in the PSA arena, I would say that people are finally listening, I think men, actually over the last five or so years, really are backing off on how often they're trying to get PSA tests, and I think doctors are doing fewer of them, although I still think a lot of doctors are doing them."* — Nancy Keating, MD, MPH, Professor of Health Care Policy at Harvard Medical School *"Because you've got members of congress who has their constituents who are very pro-screening, and feel that worry that the government is going to take that away from them for health care costs. So it's an interesting piece that you're doing, because it's not just a matter of looking at the evidence and saying it's appropriate or not."* —Deborah Kotz, FDA Reporter	

Specialists need to be on the panel/ vs. conflict of interest	"I don't know if you've come across the USPSTF recommendation …We completely disagreed with their findings, there were no oncologists, surgeons, people who were experts in the field really on that panel. So we were very vocally opposed to that announcement... ……You came across that? So they said no mammograms until 50 and then every other year, and I think they said no mammograms after the age of 72 or 74. We completely disagreed with their findings, there were no oncologists, breast surgeons, or people who were experts in the field really on that panel that made those recommendations. So we were very vocally opposed to that announcement. I actually testified at our state legislature and at other venues around how it's between a woman and her doctor, but that it is known that starting at age 40 it's the recommendation." —Patient Advocate	"I think I heard that [argument] that in the taskforce there weren't so many specialists. Let's say to some extent I agree in the sense that I do believe you need the experts of all the different specialties involved, but you could erase that by having the experts present some material and information. They may then be, for instance, secondly involved, so they don't necessarily have to vote, but you have to take care of that indeed. All the aspects come on the table, so if there is over-treatment, there should be either a psychologist talking about quality of life, or there should be a surgeon saying, "Every now and then, I see the most awful surgery I've ever performed," or whatever. So I agree with that in general terms. It's not necessary that they-- you can just present that, and then that's another independent committee shoots that way." —Harry de Koning, Professor of Evaluation of Screening, CISNET prostate modeling group
Clinician versus policy, advocacy versus activist views		
	"One of the things that I wanted to say, and I know we're a little off script, is I think some of the USPSTF, guidelines both for breast and for prostate, the consensus committee that reviewed the literature, they don't really necessarily have experts from those fields on the committees. So maybe you don't need an expert to review the raw data and the literature, but I think you need experts to assess literature, is this a good study, what are the.. and so that's just really weird…"—Clinician	"This is actually an interesting and tricky one, because to be a specialist is to have a conflict of interest on this issue. To be a radiologist, what are radiologists' bread and butter?" — Karuna Jaggar, Executive Director, Breast Cancer Action

APPENDIX N. Sources of Noncompliance to Practice Guidelines

| There are too many of them, there is no unified message | "They [guidelines] are incomplete. I review guidelines and see if they agree with other guidelines. My concern with guidelines in general is they do not speak with a common language or have a common rating system. For instance, we could take four subspecialty societies and look at guidelines, we would see some of them use capital letters, ABCD and F, we would see that others use Roman numerals with Arabic letters after them. I'm tired of this, we need to speak with a common language. We may not agree with what is spoken or said with the language, but at least we could communicate with one another across specialties. I suggest that all of the specialty societies meet with the USPSTF and develop a common language for all clinical guidelines. "—John Barry, Professor of Urology) |

	"For example if the practitioner, there's any number of... I think right now there's 12 or 13 sets of screening guidelines on... I'm not exaggerating, it's a lot..." —Clinician *"I'm not sure that's clear to patients, that there really are different guidelines. The data is difficult to interpret, I think both for the layman as well as for the doctor. So I think patients are getting mixed messages and I think a lot of people are like, "Well if they don't know, then I'm not going to bother." I wish that there was a unified message about screening. That can be confusing."* —Clinician *"People are just all over the map. Different doctors, different organizations, make different guidelines and people become confused, so I am guessing some of them screened very little, some of them are too much..."*—Oguzhan Alagoz, Professor, Industrial and Systems Engineering, University of Wisconsin-Madison, Cancer Intervention and Surveillance Modeling Network (CISNET)
Changes too fast	*"I think that everybody, we try to follow the most recent guidelines. I think one of the pitfalls is that there are probably some various doctors out there that may not stay current with the latest guidelines because things are always changing and they change so fast. So a patient might go to see a doctor who may not be up on the latest information and then they come to see me and they'll say, "My other doctor never would suggested this, or never told me this." It's a just a matter of educating people. So I think that we're definitely as family practitioners in agreement with these guidelines."* —Shelley Justa, MD, Family Practitioner *"The PSA guidelines have been revised... What does the current revision say? Because we've joked about at tumor board and criticized, but I can't remember actually what they changed it to off the top of my head right now."* —Clinician
USPSTF did a bad job communicating guidelines	*"Yes, they [USPSTF] really didn't do a good job [in communicating]. They blew it in such a...I don't mean to be negative, I think that their work is fantastic. But unfortunately their messaging ended up, I think they just didn't realize and unfortunately it didn't just do a disservice at the time, it has resonated ever since... It's really too bad that they just didn't understand the politics, it's really too bad."* —Peggy Orenstein, Health Journalist, NY Times
Specialists don't follow the guidelines	*"A tumor board, it's the experts in treatment of these various cancers. We don't talk about them often, but when they come up it's usually, I think there's I won't say lack of enthusiasm, but I think there's criticism. There's some almost, I don't want to say a missed opportunity, sort of the sense that things have gone wrong in terms of new guidelines. This is sort of vague recollection and hearsay, I think when the breast guidelines came out, like the family practice docs adopted them at OHSU fairly immediately and the radiologists were like, "Wait a second. Let's talk about this before you go and change the way we're screening OHSU patients," they wanted to try and do some more education of the family practice folks, the primary care, I shouldn't say just family practice, the primary care."* Clinician *"I'm not exactly sure how that landed, how that ended up. But I know breast and prostate were quite controversial amongst the specialists or the tumor docs and radiologists, versus the primary care folks."* —Clinician

"The thing is, the tumor boards are not the ones who are doing the screening again, it's the primary care docs. But I think the fact that various esteemed organizations in the U.S. are recommending less screening for fairly common cancers is not a good thing, in the view of the people who treat those cancers. The guidelines have been put together, and American Cancer Society I can't tell you who was on the guidelines because you'd think the Cancer Society would be the cancer experts…" —Clinician

"I would say rely on data more for that, but in general, from my reporting, what I can tell you, is that the doctors who are primary care physicians, the ones who are family physicians, they tend to be more likely to follow the USPTF guidelines, because those guidelines are aimed at that. So primary care physicians, especially the younger ones, the ones under the age of 40 or 45, are much more open to saying to patients, "There are drawbacks to screening. You need to make an informed decision. It's up to you, but I can tell you that here's what the data shows. Make a decision on your own." The older doctors, and the oncology community as a whole, are-- feel extremely-- not extremely. They're in favor of screening, and I think that-- I think there may have been an article in the New York Times on this. I forget where I ran into this." —Science Reporter

"Physician not following the guidelines, and the system, it's a totally different system in the US, because, compared to Europe for instance, makes it easier not to follow guidelines in the US than it is in Europe. So, indeed, to some extent we circumvent the physician in the guidelines and send out invitations to everyone." —Harry de Koning, Professor of Evaluation of Screening, CISNET

Difficult to translate to patients	"I have a very difficult time as the provider, being like, "You know you're going to die of your … [other disease], so we don't need to do the screening test." That's a very difficult conversation to have. I am screening simply because it's a very complicated, loaded emotional question to talk about, "You don't need screening because you're going to die of something else," that's really not an easy conversation." —Clinician

"I personally find translation of population based guidelines very difficult when that person's sitting in front of you and either they don't want to do what you're asking them to do, or conversely you're like, "You're 80 years old, you don't need this anymore," and they're like, "Well, it just makes me feel better. It gives me peace of mind. I really, really want it…"—Erin Hofstatter, School of Medicine, Assistant Professor of Medicine (Medical Oncology) and Co-Director, Genetic Counseling Program

"So I have the difficulty of trying to deal with how to present the data and what to tell them to do. I think that this probably does give them some leeway. I mean I can't insist in a way that I might have insisted previously, I will try to work with them more than I would have before these recommendations came out." — Clinician

"Yes. It's one thing to say it's not reasonable to screen after a certain age. The problem is when guidelines are set, and I think this is appropriate when guidelines are set, there's no emotion, and you don't have a patient in front of you. The guidelines are then set and then the physician that has the patient in front of her |

	has to talk to them. I think it's also important to state guidelines are guidelines, they are not mandates for practice. They're things to think about, things to refer to, points of discussion, but it doesn't necessarily mean this is how you have to practice." —Deanne Attai, Former President at American Society of Breast Surgeons, Clinical Professor of Surgery UCLA
Fear of Litigation	*"…and then suddenly I'm the gatekeeper to a screening practice that they're insisting that they want. God forbid they actually get diagnosed with a cancer and then I'm the one who stood in the way of getting that screening test. So I find that difficult, is when people are reaching their… I don't have a crystal ball to say, is this person going to go on and get a cancer and at what age, and could it have been a better outcome had I gotten a screening test. So I find it very hard to undo." —Clinician* *"I feel like as a physician I don't really have any backing. If something is covered by their insurance but I don't think they need it, I do not feel like I have any ground to stand on if I feel they don't need it… yet they want it because they think that that will make them, they're staying on top of things, and I think it gives them a sense of control. But it's not making them live longer or better…" —Clinician* *"I think breast ultrasound is a perfect example. I would say many practitioners in Connecticut routinely think of breast ultrasound when a person has dense breast tissue. But in the vast part of the U.S. breast ultrasound is either not thought of, and if it is thought of it's not covered by insurance. I don't know what the law says, but if I do not discuss some kind of supplementary screening with my patients who have dense breast tissue then I think I'm going to be held liable because now they have that mandate where it says at the bottom of the report, "You have dense breast tissue. Talk about it with your doctor." So if I get sued because a person gets a breast cancer that could have been detected on an ultrasound, that's on me, I'm liable for that. But I don't think that's the case in other states." —Erin Hofstatter, School of Medicine, Assistant Professor of Medicine (Medical Oncology) and Co-Director, Genetic Counseling Program* *"As a researcher, I can talk about overdiagnosis. I can talk about the harms of screening that we need to have more information and let people make more decisions, because, in my view, the decision to undergo mammography screening is not an obvious decision. It's not like everybody should do it.…"…But then as a clinician, when I have patients, I recognize that this is another setting. You have something that is perceived as a serious disease. I cannot put the burden on my shoulders. So you have to be optimistic, you have to be positive, or you have to be realistic, and not put them down by saying, "If you didn't go to screening, you might not have this cancer." — Clinician, Academic* *"PSA is overused because first no one wants to be blamed to miss a possible prostate cancer diagnosis and second most of the patients are ask for it. Additionally, we also know that PSA is not specific for prostate cancer and it can be increased in other prostatic diseases such as benign prostate hyperplasia or prostatitis." —Ilker Tinay, MD, Urology, Marmara University School of Medicine, Formerly: Brigham and Women's Hospital, Urology*

Problematic Language	*"It was January 1997 when I was diagnosed. So I don't think that people really…I definitely didn't understand the politics around screening and it took me a long time to understand that fully. My first article was really just about being a young woman diagnosed with cancer, and it was in fact the diametric opposite of what I wrote in 'Feel-Good War Against Cancer' because they had just had one of the studies out that showed that there was no real reason to be doing mammograms on women under 50. The way that it was put was that it didn't save enough lives. The way that's it put, I think is a problem."* —Peggy Orenstein, Journalist, NYTimes
We need individualized, tailored screening	*"I just really think that screening is not one size fits all. If we're going to make guidelines that have to be one size fits all, then I think we have to be very liberal about using them so that they catch any cancer that's possibly missed as opposed to sticking your head in the sand and not doing the screening. At the same time, if we're going to save costs and do the best we can to target screening then I think we have to be a lot better at doing the studies about risk stratification and risk modeling, and I think we need to be smarter about applying these guidelines based more on, "Do you have a family history or not?" I don't think people are savvy, based on risk factors, in tailoring screening. Yes, that'd be my only [extra] comment…"* —Clinician

APPENDIX O: List of Equations for Essay#2

"% D+"=0.3
>Units: dmnl
>Assumption: %30 of men over 40 belongs to D+ Haas et al., 2008- 25% to 40% has unsuspected PCa. Prevalence is highest among american men of caucasian and african origin, but trends are similar among all countries reporting.

Actual Starting Age for Routine Screening=SMOOTH3(Recommended Starting Age R, Public Perception Delay)
Units: Ages
The actual starting age for routine screening, as affected by recommendations and advocacy groups

age=Baseline Age+(Time-INITIAL TIME)/nr of years
Units: Ages
Constant+(Time-INITIAL TIME)/divide by this nr of years

"Age Specific Prevalence D+"=MIN(1,MAX(0,(Actual Starting Age for Routine Screening-Baseline Age)*"Slope D+"
+"Baseline D+"))
Units: dmnl

"Baseline D+"+(Actual Starting Age for Routine
>Screening-Baseline Age)*"Slope D+" Age-specific prevalance of
>"histological"(not clinical) PCa, prevalance is plotted as a
>function of host age (time). Prevalence is the number of cases
>of a particular condition that exists in a given population and
>consists of diagnosed cases plus those cases that are present
>but yet undetected.

"Age vs D+ Carter, 1990 Japan"="Table Age vs D+ Carter, 1990 Japan Histological"(age)
Units: dmnl
"Age vs D+ Carter, 1990 US Male Clinical"="Table Age vs D+ Carter, 1990 US Male Clinical"(age)
Units: dmnl
"Age vs D+ Carter, 1990 US Male"="Table Age vs D+ Carter, 1990 US Histological"(age)
Units: dmnl
"Age vs D+ Guileyardo, 1980 US Blacks"="Table Age vs D+ Guileyardo, 1980 US Blacks"(age)
Units: dmnl
"Age vs D+ Guileyardo, 1980 US Whites"="Table Age vs D+ Guileyardo, 1980 US Whites"(age)
Units: dmnl
"Age vs D+ Haas et al., 2007-all PCa"="Table Age vs D+ Haas et al., 2007-all PCa"(age)
Units: dmnl
"Age vs D+ Haas et al., 2007-clinically significant"="Table Age vs D+ Haas et al., 2007-clinically significant"(age)
Units: dmnl
"Age vs D+ Jahn et al., 2015 Asian"="Table Age vs D+ Jahn et al., 2015 Asian"(age)
Units: dmnl
"Age vs D+ Jahn et al., 2015 US Black"="Table Age vs D+ Jahn et al., 2015 US Black"(age)
Units: dmnl
"Age vs D+ Jahn et al., 2015 US White-European"="Table Age vs D+ Jahn et al., 2015 US White-European"(age)
Units: dmnl
"Age vs D+ Rebbeck et al., 2014 African Descent"="Table Age vs D+ Rebbeck et al., 2014 African Descent"(age)
Units: dmnl
"Age vs D+ Rebbeck et al., 2014 Asian Descent"="Table Age vs D+ Rebbeck et al., 2014 Asian Descent"(age)
Units: dmnl
"Age vs D+ Rebbeck et al., 2014 European Descent"="Table Age vs D+ Rebbeck et al., 2014 European Descent"(age)
Units: dmnl
"Age vs D+ Sakr et al., 1993 US White"="Table Age vs D+ Sakr et al., 1993 US White"(age)
Units: dmnl
"Age vs D+ Sakr et al., 1993. US Black"="Table Age vs D+ Sakr et al., 1993. US Black"(age)
Units: dmnl
"Age vs D+ Sakr et al., 1994 African American"="Table Age vs D+ Sakr et al., 1994 African American"(age)
Units: dmnl
"Age vs D+ Sakr et al., 1994 Caucasian American"="Table Age vs D+ Sakr et al., 1994 Caucasian American"(age)
Units: dmnl
"Age vs D+ Soos et al., 2005. Hungary"="Table Age vs D+ Soos et al., 2005. Hungary"(age)
Units: dmnl
"Age vs D+ Stamatiou, 2006. Greece"="Table Age vs D+ Stamatiou, 2006. Greece"(age)
Units: dmnl
"Age vs D+ Yao, 2002. Spain"="Table Age vs D+ Sanchez-Chapado et al., 2003. Spain"(age)

Units: dmnl

"Age vs D+ Yatani et al., 1988 Japan 1965-1979"="Table Age vs D+ Yatani et al., 1988 Japan 1965-1979"(age)

Units: dmnl

One study reported an increase in the frequency of latent
        cancers between two time perios for the same location (Haas et
        al., 2008-ref 19)

"Age vs D+ Yatani et al., 1988 Japan 1982-1986"="Table Age vs D+ Yatani et al., 1988 Japan 1982-1986"(age)

Units: dmnl

Age vs Prevalence Model=MIN(1,MAX(0,"Baseline D+"+(Time-INITIAL TIME)*"Slope D+"*age year convert))

Units: dmnl

Sanchez chapado et al/, 2003--slope for AA and CA, african
        american and caucasian americans is 1.38. R2==0.96, for CM 0.75.
        Fig. 3. Comparison of the prevalence of CaP in Caucasian
        Mediterranean (CM) men, Caucasian-American (CA) men, and
        African-American(AA)men

age year convert=1

Units: Ages/Year

arg normal=$ax/((1+bx^2)^{0.5})$

Units: dmnl

AUC= INTEG (Change in AUC,0)

Units: dmnl

Area Under the Curve. AUC is interpreted as the average value of
        sensitivity for all possible values of specificity, is a measure
        of the overall performance of a diagnostic test. AUC can take on
        any value between 0 and 1, where a bigger value suggests the
        better overall performance of a diagnostic test

ax=("Mu D+"-"Mu D-")/"Sigma D+"

Units: dmnl

Baseline Age=25

Units: Ages

Estimates in the literature usually starts for age 30+--Etzioni
        FHCRC model PSA growth intercept= age 35 35

"Baseline D+"=0

Units: dmnl

Baseline prevalance of PCa for men at age 25 (OR BASELINE AGE).
        Changes between 1-8% for men in their 20-30's, based on race
        (Jahn et al., 2015, Markov model assumptions, 1994). Previous
        equation:Table for Effect of Age on D+(Actual Starting Age for
        Routine Screening) 0.04

BENEFITS=SUM(Unit Benefit[testoutcome!,diseasestate!]*Probability of Test Outcome[testoutcome
!,diseasestate!])

Units: dmnl

Total amount of benefits for screening

bx="Sigma D-"/"Sigma D+"

Units: dmnl

"CDF D+ Jacobsen 1996, 50-59"="Table D+ for CDF Jacobsen 1996, 50-59"(Cutoff X)/100

Units: dmnl

"CDF D+ Jacobsen 1996, 60-79"="Table D+ for CDF Jacobsen 1996, 60-79"(Cutoff X)/100

Units: dmnl

"CDF D+ Porter et al., 2006 men 60+"="Table D+ for CDF Porter et al., 2006 men 60+"(Cutoff X)

Units: dmnl

"CDF D+ Zhang et al., 2012"="Table D+ for CDF Zhang et al., 2012"(Cutoff X)

Units: dmnl

"CDF D- Jacobsen 1996, 50-59"="Table D- for CDF Jacobsen 1996, 50-59"(Cutoff X)/100

Units: dmnl

"CDF D- Jacobsen 1996, 60-69"="Table D- for CDF Jacobsen 1996, 60-69"(Cutoff X)/100

Units: dmnl

"CDF D- Jacobsen 1996, 70-79"="Table D- for CDF Jacobsen 1996, 70-79"(Cutoff X)/100

Units: dmnl

"CDF D- Porter et al., 2006 men 40-49"="Table D- for CDF Porter et al., 2006 men 40-49"(Cutoff X)/100

Units: dmnl

"CDF D- Porter et al., 2006 men 60-69"="Table D- for CDF Porter et al., 2006 men 60-69"(Cutoff X)/100
Units: dmnl
"CDF D- Porter et al., 2006 men 70-79"="Table D- for CDF Porter et al., 2006 men 70-79"(Cutoff X)/100
Units: dmnl
"CDF D- Zhang et al., 2012"="Table D- for CDF Zhang et al., 2012"(Cutoff X)
Units: dmnl
CDF of T="CDF of Threshold for D+"*"% D+"+"CDF of Threshold for D-"*(1-"% D+")
Units: dmnl
"CDF of Threshold for D+"=(NCDF((LnX-"Mu D+")/(2*"Sigma D+")^0.5))
Units: dmnl
Cumulative density of the D+ distribution at cutoff point C--LOGNORMAL.
"CDF of Threshold for D-"=(NCDF((LnX-"Mu D-")/(2*"Sigma D-")^0.5))
Units: dmnl
Cumulative density of the D- distribution at cutoff point C--LOGNORMAL.
"CDF Vickers et al. 2010"="Table for CDF Vickers et al. 2010"(Cutoff X)/100
Units: dmnl
Change in AUC=TP/divide by this nr of years*"PDF of Threshold for D-"
Units: 1/Year
Change in R=(Indicated Starting Age for Screening-Recommended Starting Age R)/Time to Adj R
*R Switching
Units: Ages/Year
Change in Threshold=(Desired Threshold-Threshold T)/Time to Adj T*Threshold Switching
Units: 1/Year
Yearly rate of change of the Threshold value T
Constant=1e-013
Units: dmnl
-3
Cutoff X=Constant+(Time-INITIAL TIME)/divide by this nr of years
Units: dmnl
This used to be: Constant+(Time-INITIAL TIME)/divide by this
            number of years= -10+Time/2 Threshold value T for the Test
            Outcome.
Data for Threshold T([(1990,0)-(2040,4)],(1990,4),(2000,4))
Units: 1/Year
Effect of lowering PSA cutoffs-- Some investigators have
            suggested using a lower PSA cutoff because some men with PSA
            levels below 4 ng/mL and normal digital rectal examinations are
            found to have prostate cancer
            [52-55].http://www.uptodate.com/contents/screening-for-prostate-c
            ancer
Desired Threshold= Function for desired T(Threshold T*Effect of HBR on T*Eff Ext Pressure on T)
Units: dmnl
Desired Threshold value implied by the HBR and other external pressures (other advocacy and interest groups)
diseasestate: Dplus,Dminus
divide by this nr of years=1
Units: Year
Doctors Weighing on T=1
Units: dmnl
Public doesnt have much influence on T, its more of a doctors
            decision.. If different thresholds are announced, which one
            doctors are following, on the average. Base initial assumption
            is 40% professionals, 60% other medical and advocacy groups.
duration=FINAL TIME-INITIAL TIME
Units: Year
Eff Ext Pressure on C2=1+StrengthEffExtPonT*(External pressures-1)
Units: dmnl
external pressures*sensitivity to external pressure+(1-sensitivity to external pressure)
Eff Ext Pressure on T= Relative Influence of Advocacy Groups^StrengthEffExtPonT
Units: dmnl
Effect of external pressures on Cutoff value C
Effect of HBR on Indicated Age for Screening=1+HBR Multiplier*(Perceived HBR-1)

168

Units: dmnl

Effect of HBR on T= Perceived HBR^StrengthEffofHBRonT

Units: dmnl

Effect of Harms to Benefits Ratio (HBR) on Cutoff value C

Effective Recommended Starting Age=1

Units: Ages

Public Weighing on R*Recommended Starting Age R

Effective Threshold=Doctors Weighing on T*Threshold T

Units: dmnl

In signal detection theory, overall performance depends both on
accuracy (otherwise known as 'sensitivity') of judgment and
on the threshold (otherwise known as 'bias').

"Empirical AUC, Thompson et al., 2005"=0.678

Units: dmnl

AUC is interpreted as the average value of sensitivity for all
possible values of specificity, is a measure of the overall
performance of a diagnostic test.

Empirical AUC2=0.74

Units: dmnl

Vickers et al., 2010. BMJ. Any Prostate Cancer vs No Prostate Cancer.. http://www.ncbi.nlm.nih.gov/pubmed/15998892

Empirical Mean and Median=1

Units: dmnl

Median is 1. from Wilt et al.,
2014.http://onlinelibrary.wiley.com/doi/10.1002/pros.20417/abstra
ct Mean=1.84 in etzioni et al., 2004?

Empirical NPV=0.85

Units: dmnl

Negative predictive value--The Prostate Cancer Prevention Trial,
which biopsied men with normal PSA levels, estimated a negative
predictive value of 85 percent for a PSA value ≤4.0 ng/mL
[51].
http://www.uptodate.com/contents/screening-for-prostate-cancer

Empirical PPV=0.3

Units: dmnl

Positive predictive value-- The test performance statistic that
has been best characterized by screening studies is the positive
predictive value: the proportion of men with an elevated PSA who
have prostate cancer.

Empirical Sens=1

Units: dmnl

Wilt et al., 2014. A major drawback of PSA for screening and
early detection is its low specificity. In 65% to 75% of men
with an elevated PSA level (>3 ng/mL), no cancer is found on
biopsy (34), and in 80%, no high-grade (Gleason score >7)
potentially lethal cancer is found

Empirical TPR="Table ROC for PSA, Thompson et al., 2005 AUC=0.678"("False Pos Rate (FPR)")

Units: dmnl

"expMeanD+"=exp("Mu D+")

Units: dmnl

"expMeanD-"=exp("Mu D-")

Units: dmnl

External pressures=1

Units: dmnl

External pressures (dimensionless)

The GAMMA function is a generalization of the factorial function
that works on all positive values of X. For an integer N the
factorial of N is equal to the GAMMA function of N+1. SOURCE:
http://www.ventanasystems.co.uk/forum/viewtopic.php?f=2&t=4206.

"False Neg Rate (FNR)"=1-"True Pos Rate (TPR)"

Units: dmnl

False negative rate. False negatives are much less frequent, but

potentially more serious, because they may result in an
aggressive malignancy.

"False Pos Rate (FPR)"=1-(NCDF((LnEffThreshold-"Mu D-")/(2*"Sigma D-")^0.5))
Units: dmnl
False positive rate, also known as the "False positive
fraction". =P(T+/D-).FPR is defined as the proportion of healthy
subjects incorrectly classified as diseased. False positives,
defined as men who are referred for biopsies or other additional
diagnostic treatments but who are later found not to have tumors
are clearly the most frequent error.

FINAL TIME = 2040
Units: Year
The final time for the simulation.
Formal Threshold=Threshold Table(Time)
Units: dmnl
Total PSA using thresholds of 4.0 and 2.5 ng/mL has been used
for screening men.For total PSA values between 4 and 10 ng/mL, a
prostate biopsy is preferred, but lowering the threshold to 2.5
ng/mL has been suggested

FP=1-"CDF of Threshold for D-"
Units: dmnl
Function for desired T(
[(0,0)-(1000,1000)],(0,0),(0.2,0.2),(0.3,0.3),(0.4,0.4),(1,1),(1,1),(2,2),
(3,3),(4,4),(5,5),(1000,1000))
Units: dmnl
Table function for PSA Threshold
group:prof,advoc
Guideline Start Year=1990
Units: Year
HARMS=SUM(Unit Cost[testoutcome!,diseasestate!]*Probability of Test Outcome[testoutcome
!,diseasestate!])
Units: dmnl
Total amount of harms for screening
Harms to Benefits Ratio=HARMS/BENEFITS
Units: dmnl
"Harms to Benefits Ratio". It represents the real/actual ratio of harms to benefits of screening.
HBR Multiplier=0.3
Units: dmnl
Multiplier for the effect of HBR on starting age of screening.
HBR Reference=1
Units: dmnl
Reference value of HBR
HBR Trans Delay=10
Units: Year
Scientific evidence translation delay Time constant for the HBR (harms to benefits ratio) perception delay
Indicated Starting Age for Screening=Actual Starting Age for Routine Screening*Effect of HBR on Indicated Age for
Screening
Units: Ages
INIT Nr of Healthy Women= INITIAL(3.55e+007)
Units: People
7.1e+007 is the population of US in 1975. 50% is women
INIT Nr of Women Survived from Cancer= INITIAL(5000)
Units: People
INIT Nr of Women Undiagnosed with Cancer= INITIAL(5.5e+006)
Units: People
INIT Nr of Women with Diagnosed Cancer= INITIAL(50000)
Units: People
INIT R=50
Units: Ages
Initial recommended starting age
INIT Threshold=4

Units: dmnl
Set of initial values of the Threshold T for different groups 0.5,0.5;
INITIAL TIME = 1980
Units: Year
The initial time for the simulation.
LnEffThreshold=LN(Effective Threshold)
Units: dmnl
LnX=LN(Cutoff X)
Units: dmnl
Natural logarithm of the Cutoff value X. See Inoue an Etzioni et al., 2004. LN(Cutoff X+1)
"Marginal Subst Rate (MSR)"="True Pos Rate (TPR)"/"False Pos Rate (FPR)"
Units: dmnl
TPR/FPR. A small increase in the selection rate would result in
                about MSR times additional false positives for every true
                positive added. Marginal Substitution Rate- Stewart, 2008.
"mean D+"=exp("Mu D+"+"Sigma D+"^2/2)
Units: dmnl
LN("Mu D+")-"Sigma D+"^2/2
"mean D-"=exp("Mu D-"+"Sigma D-"^2/2)
Units: dmnl
LN("Mu D-")-"Sigma D-"^2/2
"Mean PSA Etzioni, 2004"=1.84
Units: ng/ml
Etzioni et al., 2014. Cancer Epidemiology and Biomarkers.
                http://www.ncbi.nlm.nih.gov/pubmed/15466981 Mean PSA is 1.84
                ng/ml, at mean age 60. 5.50 ng/ml for cancer patients?
"median D+"=exp("Mu D+")
Units: dmnl
LN("Mu D+")-"Sigma D+"^2/2
"median D-"=exp("Mu D-")
Units: dmnl
LN("Mu D-")-"Sigma D-"^2/2
"Mu D+"=1
Units: dmnl
1- 2-1.2 Old value=1.9. Mean value of the distribution of the
                test outcome for the diseased (D+) population.
"Mu D-"=0.3
Units: dmnl
Mean value of the distribution of the test outcome for the healthy (D-) population.
"Neg Like Ratio (NLR)"=(1-"True Pos Rate (TPR)")/(1-"False Pos Rate (FPR)")
Units: dmnl
The ratio between the probability of a negative test result
                given the presence of the disease and the probability of a
                negative test result given the absence of the disease, i.e. =
                False negative rate / True negative rate = (1-Sensitivity) /
                Specificity
"Neg Pred Value (NPV)"="True Neg Rate (TNR)"/("True Neg Rate (TNR)"+"False Neg Rate (FNR)")
Units: dmnl
The probability that the disease is not present when the test is
                negative (expressed as a percentage). NPV= d / (b+d) =
                specs*(1-prevalence)/(1-sens)*prevalence+specs*(1-prevalence)
Net Increase Fract=0.016
Units: 1/Year
The fractional increase rate of women in the US. Average of 1.6%/year from 1975 to 1996.
nr of years=1
Units: Year/Ages
Optimal=1
Units: dmnl
Optimal ROC=
        IF THEN ELSE(Time>0, 1 , 0)
Units: dmnl

PDF of T="% D+"*"PDF of Threshold for D+"+(1-"% D+")*"PDF of Threshold for D-"
Units: dmnl
"PDF of Threshold for D+"=1/(Cutoff X*"Sigma D+"*(2*PI)^0.5)*exp((-1)*((LnX-"Mu D+")^2)/(2*"Sigma D+"^2))
Units: dmnl
Probability density function of Threshold T for diseased (D+)
               population---LOGNORMAL PDF of PSA distribution for D+
               population. 1/("Stdev D+"*(2*PI)^0.5)*exp((-1)*((Cutoff X-"Mean
               D+")^2)/(2*"Stdev D+"^2)) for NORMAL
"PDF of Threshold for D-"=1/(Cutoff X*"Sigma D-"*(2*PI)^0.5)*exp((-1)*((LnX-"Mu D-")^2)/(2*"Sigma D-"^2))
Units: dmnl
Probability density function of Threshold T for healthy (D-)
               population--LOGNORMAL. PDF of PSA distribution for D-
               population. 1/("Stdev D-"*(2*PI)^0.5)*exp((-1)*((Cutoff_X-"Mean
               D-")^2)/(2*"Stdev D-"^2)) for NORMAL
Perceived HBR=SMOOTH3(Harms to Benefits Ratio,HBR Trans Delay)
Units: dmnl
"Perceived" Harms to Benefits Ratio (HBR) is the exponentially smoothed value of the "actual" HBR
PI=3.14159
Units: dmnl
"Pos Like Ratio (PLR)"="True Pos Rate (TPR)"/"False Pos Rate (FPR)"
Units: dmnl
The ratio between the probability of a positive test result given the presence of the disease and the probability of a
               positive test result given the absence of the disease
"Pos Pred Value (PPV)"="True Pos Rate (TPR)"/("True Pos Rate (TPR)"+"False Pos Rate (FPR)")
Units: dmnl
The probability that the disease is present when the test is positive (expressed as a percentage). PPV = a / (a+c) =
               sens*prevalence/sens*prevalence+(1-specificity)*(1-prevalence)
Present Time=IF THEN ELSE(Time=2013 , 200 , 0)
Units: Year
Probability of Disease[Dplus]="Age Specific Prevalence D+"
Probability of Disease[Dminus]=1-"Age Specific Prevalence D+"
      Units: dmnl
      Prevalence of cancer in the target population. Data for D+
               doesnt exist, and usually the data that comes from autopsy
               series is used to this purpose.
Probability of Test Outcome[testoutcome,diseasestate]=Probability of Test Outcome Conditioned on Disease
State[testoutcome,diseasestate]*Probability of Disease[diseasestate]
Units: dmnl
Probability of the test outcome
Probability of Test Outcome Conditioned on Disease State[Tplus,Dplus]=Sensitivity
Probability of Test Outcome Conditioned on Disease State[Tplus,Dminus]=1-Specificity
Probability of Test Outcome Conditioned on Disease State[Tminus,Dplus]=1-Sensitivity
Probability of Test Outcome Conditioned on Disease State[Tminus,Dminus]=Specificity
      Units: dmnl
      Probability of the test outcome conditioned on disease state
Public Perception Delay=2
Units: Year
Patients perspective---The average time required to perceive/
               and comply with the recommendations for routine screening.
               1-Scientific data accumulation, translation and 2-Public
               perception delays are the major delays in evidence based
               guideline creation.
Public Weighing on R=1
Units: dmnl
Weight put on evidence base for the starting age of routine
               screening (as opposed to advocated starting age)
R Switching=IF THEN ELSE(Time>Guideline Start Year,Switch R, 0)
Units: dmnl
1986 is the year PSA screening has started.
Recommended Starting Age R= INTEG (Change in R,INIT R)
Units: Ages

Reference HBR=1
Units: dmnl
Reference Harms to Benefits Ratio (HBR) ==1
Relative Influence of Advocacy Groups=1
Units: dmnl
Dimensionless relative strength of advocacy groups--base case value is 1--strength of advocacy groups in 1975 stock of
PP. which changes between 0-1
"ROC for PSA Etzioni et al., 2004"="Table ROC for PSA Etzioni et al., 2004"(FP)
Units: dmnl
"ROC for PSA Jacobsen et al., 1996 age 50-59"="Table ROC for PSA Jacobsen et al., 1996 age 50-59"(FP)
Units: dmnl
"ROC for PSA Jacobsen et al., 1996 age 60-69"="Table ROC for PSA Jacobsen et al., 1996 age 60-69"(FP)
Units: dmnl
"ROC for PSA Jacobsen et al., 1996 age 70-79"="Table ROC for PSA Jacobsen et al., 1996 age 70-79"(FP)
Units: dmnl
"ROC for PSA Jacobsen et al., 1996 D+"="Table ROC for PSA Jacobsen et al., 1996 AUC=0.83"(FP)
Units: dmnl
"ROC for PSA Jacobsen et al., 1996"="Table ROC for PSA Jacobsen et al., 1996 AUC=0.72"(FP)
Units: dmnl
"ROC for PSA Thompson et al., 2005"="Table ROC for PSA, Thompson et al., 2005 AUC=0.678"(FP)
Units: dmnl
"ROC for PSA, Ahn et al."="Table ROC for PSA, Ahn et al. 2014 AUC=0.577"(FP)
Units: dmnl
"ROC for PSA, Ferro et al., 2015"="Table ROC for PSA, Ferro et al., 2015"(FP)
Units: dmnl
"ROC for PSA, Steuber et al., 2008"="Table ROC for PSA, Steúber et al., 2008"(FP)
Units: dmnl
"ROC for PSA, Thompson et al., 2005 Gleason>7 or no PCa"="Table ROC for PSA, Thompson et al., 2005 Gleason>7 or no
PCa"(FP)
Units: dmnl
"ROC for PSA, Thompson et al., 2005 Gleason>8 or no PCa"="Table ROC for PSA, Thompson et al., 2005 Gleason>8 or no
PCa"(FP)
Units: dmnl
"ROC for PSA, Underwood et al. 2012"="Table ROC for PSA, Underwood et al. 2012"(FP)
Units: dmnl
SAVEPER = TIME STEP
Units: Year [0,?]
The frequency with which output is stored.
Screening Start Year=1985
Units: Year
The year PSA screening has started, 1985 or 1986, some models
                took it as 1988. Formal thresholds started in 1992 with formal
                guidelines, but even before consensus was on 4 ng/ml.
Sensitivity="True Pos Rate (TPR)"
Units: dmnl
true positives/[true positives+false negatives]. Sensitivity of
                the screening test. In signal detection theory, overall
                performance depends both on accuracy (otherwise known as
                'sensitivity') of judgment and on the threshold (otherwise
                known as 'bias').
"Sigma D+"=0.6
Units: dmnl
0.6- 0.8-0.7 Standard deviation of the distribution of the test
                outcome for the healthy (D+) population. UNKNOWN, but should be
                higher than STDEV(D-)
"Sigma D-"=0.4
Units: dmnl
0.5 Standard deviation of the distribution of the test outcome for the healthy (D-) population. UNKNOWNN.used to be
0.16, 0.3, 0.85, 0.6
"Slope D+"=0.012
Units: 1/Ages

Rate of change in prevalance per year, allows adjustments to real underlying prevalance of PCa, which is estimated by autopsy series.

Specificity=1-"False Pos Rate (FPR)"

Units: dmnl

Specificity of the test result. true negatives/[true negatives+false positives]) =d/(d+c)

StrengthEffExtPonT=0

Units: dmnl

Sensitivity of External Pressure's effect on Threshold T

StrengthEffofHBRonT=0.3

Units: dmnl

Sensitivity of BHR ratio's effect on PSA Threshold T.

Switch R=1

Units: dmnl

Switch T=1

Units: dmnl

"Table Age vs D+ Carter, 1990 Japan Histological"([[(0,0)-(100,1)],(25,0),(30.003,0.00613282),(40,0.0195836),(50,0.0844109),60,0.151684),(70,0.260475),(80,0.398689),(100,0.3987))

Units: dmnl

Carter-- from Cowen, 1994 Markov model The pathologic prevalance
                of PCa per 100.000 US males at a given age.

"Table Age vs D+ Carter, 1990 US Histological"([[(0,0)-(100,1)],(25,0),(30,0.0097),(35,0.014),(40,0.0203),(45,0.0295),(50,0.0428),(55,0.0621),(60,0.09),(65,0.1306),(70,0.1895),(75,0.2749),(80,0.3988),(100,0.3988))

Units: dmnl

"Table Age vs D+ Carter, 1990 US Male Clinical"([[(0,0)
(100,0.1)],(25,0),(50,0),(55,0.00123712),(60,0.00353735),(65,0.00772406),(70,0.0140747),(75,0.0234018),(80,0.032992),(100,0.03299))

Units: dmnl

"Table Age vs D+ Guileyardo, 1980 US Blacks"([[(25,0)-(100,1)],(25,0.2),(52.5,0.2),(65,0.344),(75,0.442),(100,0.442))

Units: dmnl

US blacks, 1980. n=207, mean 31.4%

"Table Age vs D+ Guileyardo, 1980 US Whites"([[(25,0)-(100,1)],(25,0.23),(52.5,0.23),(65,0.316),(75,0.407),(100,0.407))

Units: dmnl

"Table Age vs D+ Haas et al., 2007-all PCa"(
        [(25,0)-(90,1)],(25,0.04),(30,0.0461538),(34.6531,0.0564103),(40.0408,0.0769231
),(43.8367,0.0974359),(50.6939,0.141026),(55.7143,0.184615),(61.102,0.241026
),(66.1225,0.307692),(70.898,0.371795),(75.3061,0.438462),(81.7959,0.548718
),(86.9388,0.628205),(88.6531,0.653846))

Units: dmnl

"Table Age vs D+ Haas et al., 2007-clinically significant"(
        [(25,0)-(90,1)],(25,0),(30,0.0025641),(34.1633,0),(38.0816,0.00769231),(43.5918
,0.0025641),(48.4898,0.0102564),(54.4898,0.0230769),(59.0204,0.0410256),(63.6735
,0.0666667),(67.9592,0.120513),(71.6327,0.166667),(75.1837,0.235897),(78.3673
,0.312821),(82.1633,0.420513),(85.2245,0.520513),(87.9184,0.605128),(89.0204
,0.635897))

Units: dmnl

"Table Age vs D+ Jahn et al., 2015 Asian"(
        [(0,0)-(100,1)],(25,0.0209836),(35,0.00786885),(45,0.0288525),(55,0.0813115
),(65,0.146885),(75,0.212459),(85,0.288525),(100,0.2885))

Units: dmnl

Prostate cancer risk as a function of age, Jahn et al., 2015 Int
                J of Cancer.
                http://onlinelibrary.wiley.com/doi/10.1002/ijc.29408/abstract

"Table Age vs D+ Jahn et al., 2015 US Black"(
        [(0,0)-(100,1)],(25,0.0708197),(35,0.302951),(45,0.352787),(55,0.461639),(
65,0.472131),(75,0.504918),(100,0.5049))

Units: dmnl

Prostate cancer risk as a function of age, Jahn et al., 2015 Int
                J of Cancer.
                http://onlinelibrary.wiley.com/doi/10.1002/ijc.29408/abstract
                Although about 80 percent of detected cancers are considered

174

clinically important based on tumor size and grade [157], these
are relatively crude prognostic markers. Autopsy series in men
who died from other causes have shown a 30 to 45 percent
prevalence of prostate cancer in men in their fifties and an 80
percent prevalence in men in their seventies [158-160]. Jahn et
al., 2015.

"Table Age vs D+ Jahn et al., 2015 US White-European"([[(25,0)-
(100,1)]],(25,0.0413),(35,0.1573),(45,0.2341),(55,0.2243),(65,0.2926),(75,0.3593),(85,0.4761),(100,0.4761))
Units: dmnl
Prostate cancer risk as a function of age, Jahn et al., 2015
"Table Age vs D+ Rebbeck et al., 2014 African Descent"([[(0,0)-
(100,1)]],(25,0.016),(35,0.355),(45,0.247),(55,0.39),(65,0.567),(100,0.567))
Units: dmnl
Prostate cancer risk as a function of age.
            http://www.ncbi.nlm.nih.gov/pubmed/25347377 page 7- panel 3.
            mean=26.2%
"Table Age vs D+ Rebbeck et al., 2014 Asian Descent"([[(25,0)-
(95,1)]],(25,0),(35,0.04),(45,0.063),(55,0.173),(65,0.177),(75,0.254
),(85,0.332),(95,0.5))
Units: dmnl
Prostate cancer risk as a function of age.
            http://www.ncbi.nlm.nih.gov/pubmed/25347377 page 7- panel 1.
            mean=19.9%
"Table Age vs D+ Rebbeck et al., 2014 European Descent"([[(0,0)-
(95,1)]],(25,0.05),(35,0.084),(45,0.15),(55,0.269),(65,0.333),(75,0.354
),(85,0.49),(95,0.911))
Units: dmnl
Prostate cancer risk as a function of age.
            http://www.ncbi.nlm.nih.gov/pubmed/25347377 page 7- panel 2.
            mean=26.7%
"Table Age vs D+ Sakr et al., 1993 US White"([[(25,0)-(100,0.9)]],(25,0.08),(35,0.31),(45,0.37),(55,0.44),(65,0.65),(75,0.83
),(100,0.83))
Units: dmnl
REAL D+ is UNKNOWN, we use estimates coming from autopsy series.
            http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2706483/ Haas et
            al., 2008. The Worldwide Epidemiology of Prostate Cancer:
            Perspectives from Autopsy Studies--DATA for US White Sakr WA,
            Haas GP, Cassin BF, Pontes JE, Crissman JD. The frequency of
            carcinoma and intraepithelial neoplasia of the prostate in young
            male patients. J Urol. 1993;150(2 Pt 1):379-385. [PubMed] Table
            age groups 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90
"Table Age vs D+ Sakr et al., 1993. US Black"(
        [(25,0)-(100,0.9)]],(25,0.08),(35,0.31),(45,0.43),(55,0.46),(65,0.7),(75,0.81),(100,0.81))
Units: dmnl
REAL D+ is UNKNOWN, we use estimates coming from autopsy series.
            http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2706483/ Haas et
            al., 2008. The Worldwide Epidemiology of Prostate Cancer:
            Perspectives from Autopsy Studies--DATA for US Black Sakr WA,
            Haas GP, Cassin BF, Pontes JE, Crissman JD.
"Table Age vs D+ Sakr et al., 1994 African American"(
        [(0,0)-(100,1)]],(25,0.03),(35,0.26),(45,0.29),(55,0.44),(65,0.67))
Units: dmnl
overall--0.23, in Rebeck et al., 2014 summary n small, not very reliable
"Table Age vs D+ Sakr et al., 1994 Caucasian American"([[(0,0)-
(100,1)]],(25,0),(35,0.33),(45,0.36),(55,0.62),(65,0.6),(100,0.6))
Units: dmnl
overall--0.36, in Rebeck et al., 2014 summary-- overall 0.36
"Table Age vs D+ Sanchez-Chapado et al., 2003. Spain"(
        [(25,0)-(100,0.9)]],(25,0.0358),(35,0.0882),(45,0.1428),(55,0.238),(65,0.317),(75,0.333),(100,0.333))
Units: dmnl
29. Sanchez-Chapado M, Olmedilla G, Cabeza M, Donat E, Ruiz A.

175

Prevalence of prostate cancer and prostatic intraepithelial
neoplasia in Caucasian Mediterranean males: an autopsy study.
Prostate. 2003;54(3):238-247. [PubMed]
http://www.ncbi.nlm.nih.gov/pubmed/12518329 in Haas et al.,
2008.

"Table Age vs D+ Soos et al., 2005. Hungary"([[(25,0)-(100,1)],(25,0),(35,0.15),(45,0.266),(55,0.321),(65,0.5),(75,0.647
),(85,0.866),(100,1))
Units: dmnl
31. Soos G, Tsakiris I, Szanto J, Turzo C, Haas GP, Dezso B. The
prevalence of prostate carcinoma and its precursor in Hungary:
an autopsy study. Eur Urol. 2005;48(5):739-744.
"Table Age vs D+ Stamatiou, 2006. Greece"([[(25,0)-(95,1)],(25,0),(35,0),(45,0.026),(55,0.052),(65,0.138),(75,0.305),
(85,0.4),(95,0.562))
Units: dmnl
30. Stamatiou K, Alevizos A, Perimeni D, Sofras F, Agapitos E.
Frequency of impalpable prostate adenocarcinoma and precancerous
conditions in Greek male population: an autopsy study.
"Table Age vs D+ Welch book"=1
Units: dmnl
Prostate Cancer Reservoir Found in Men after Accidental Death,
Welch, Schwartz and Woloshin, 2011- Book page 48.
"Table Age vs D+ Yatani et al., 1988 Japan 1965-1979"(
[(0,0)-(200,1)],(25,0),(55,0.1133),(65,0.2013),(75,0.2458),(85,0.404),(100,0.404))
Units: dmnl
"Table Age vs D+ Yatani et al., 1988 Japan 1982-1986"(
[(25,0)-(100,0.9)],(25,0),(35,0.2),(45,0.13),(55,0.22),(65,0.35),(75,0.41),(85,0.48),(100,0.48))
Units: dmnl
"Table D+ for CDF Jacobsen 1996, 50-59"(
[(0,0)-(100,100)],(0,0),(0.412421,5.49478),(1.42036,11.1563),(2.23094,17.1631
),(4.14617,27.9715),(4.4132,17.3162),(5.55227,34.145),(5.63423,28.1305),(7.45127
,39.2834),(7.73305,33.7826),(8.64084,39.1013),(8.65706,44.7713),(10.64,44.5825
),(10.6582,50.9397),(11.3514,50.5901),(11.4648,55.572),(14.739,56.0594),(14.8509
,60.5258),(20.406,60.9935),(20.8179,66.3165),(22.305,66.1319),(22.4219,72.3165
),(23.4278,77.2907),(23.8098,72.1328),(26.2066,77.9541),(26.4133,80.8734),(
29.6913,82.7352),(38.3197,82.8329),(38.5333,88.1576),(43.2101,93.6157),(60.5655
,93.6385),(1000,100))
Units: dmnl
Jacobsen et al. 1996- http://www.ncbi.nlm.nih.gov/pubmed/8944739
This population-based case-control study was conducted in
Olmsted County, Minnesota
"Table D+ for CDF Jacobsen 1996, 60-79"(
[(0,0)-(100,100)],(0,0),(1.30939,7.03348),(1.59952,4.45365),(2.41305,11.4914
),(3.23768,10.8543),(3.32117,16.9246),(4.776,17.0267),(4.8019,26.0758),(6.00769
,31.5637),(6.55201,36.9428),(7.67595,36.9332),(7.75846,42.6599),(8.75902,45.7441
),(8.9672,49.1788),(10.3016,53.4056),(10.4492,58.7881),(11.5797,61.0694),(12.5152
,64.4978),(12.9858,67.2429),(13.2562,69.3024),(16.0346,69.8513),(16.2402,72.3696
),(17.5003,73.7334),(18.5012,76.9321),(20.8878,79.2026),(21.7539,81.4861),(
24.2004,81.5797),(29.626,83.0222),(32.6084,85.5166),(38.161,85.1253),(38.4336
,87.9866),(43.1948,88.2894),(46.5038,89.4064),(56.2239,89.7811),(57.6843,91.8304
),(59.998,91.696),(1000,100))
Units: dmnl
Jacobsen et al. 1996- http://www.ncbi.nlm.nih.gov/pubmed/8944739
"Table D+ for CDF Porter et al., 2006 men 60+"(
[(0,0)-(25,1)],(0,0),(1,0.67),(2,0.74),(3,0.8),(4,0.85),(7,0.95),(10,0.98)
,(25,1),(100,1))
Units: dmnl
"Table D+ for CDF Zhang et al., 2012"([[(0,0)-
(20,1)],(0,0),(1,0.138),(2.5,0.367),(4,0.559),(7,0.785),(10,0.888),(50,0.999),(100,1))
Units: dmnl
PSA tests done in Olmsted County, Minnesota from 1983 to 2005.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3288242/

"Table D- for CDF Jacobsen 1996, 50-59"([[(0,0)-(10,100)]],(0,0),(0.45,30.2409),(0.679445,64.1413),(1.16191,71.01),(
1.84502,78.6789),(2.06139,84.9772),(3.75064,97.6776),(7.06027,99.0237),(9.50748
,99.3463),(12.2191,99.6667),(1000,100))
Units: dmnl
Jacobsen et al. 1996- http://www.ncbi.nlm.nih.gov/pubmed/8944739
"Table D- for CDF Jacobsen 1996, 60-69"([[(0,0)-
(100,100)]],(0,0),(0.645896,29.3188),(1.31895,56.5756),(3.10938,81.5317
),(3.9787,84.9607),(4.05891,89.8856),(4.79961,94.5757),(5.79591,96.1709),(6.19751
,97.8856),(7.39117,99.1354),(9.44136,99.3469),(1000,100))
Units: dmnl
Jacobsen et al. 1996- http://www.ncbi.nlm.nih.gov/pubmed/8944739
"Table D- for CDF Jacobsen 1996, 70-79"([[(0,0)-(80,100)]],(0,0),(0.976794,29.4305),(1.12312,34.3549),(1.4632,37.6739
),(1.82557,48.7819),(2.12805,62.067),(3.36368,77.9786),(3.89947,80.3795),(4.70202
,83.5799),(5.1799,88.8451),(5.51932,91.935),(6.45246,94.5615),(7.51586,96.4997
),(8.24705,97.868),(9.8351,98.3126),(1000,100))
Units: dmnl
Jacobsen et al. 1996- http://www.ncbi.nlm.nih.gov/pubmed/8944739
"Table D- for CDF Porter et al., 2006 men 40-49"([[(0,0)-
(20,100)]],(0,0),(0.5,32.3),(1,73.3),(2,95.1),(3,97.8),(4,98.4),(100,100))
Units: dmnl
"Table D- for CDF Porter et al., 2006 men 60-69"([[(0,0)-
(20,100)]],(0,0),(0.5,20.4),(1,50.2),(2,76.3),(3,87),(4,94.4),(100,100))
Units: dmnl
"Table D- for CDF Porter et al., 2006 men 70-79"([[(0,0)-(10,100)]],(0,0),(0.5,11.9),(1,33),(2,51.7),(3,65.8),(4,79),(12,100)
,(100,100))
Units: dmnl
"Table D- for CDF Zhang et al., 2012"([[(0,0)-(20,1)]],(0,0),(1,0.471),(2.5,0.808),(4,0.909),(7,0.968),(10,0.983),
(50,1),(100,1))
Units: dmnl
PSA tests done in Olmsted County, Minnesota from 1983 to 2005.
                There are a total of 11,872 men underwent PSA testing during
                this timeframe with a total of 50,589 PSA test results --page 5.
                http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3288242/
"Table for CDF Vickers et al. 2010"([[(0,0)-(15,99)]],(0,0),(0.43,10),(0.65,25),(1.06,50),(1.5,67),(1.92,75),(2.12
,80),(3.4,90),(5.17,95),(14.8,99),(50,99.9),(1000,100))
Units: dmnl
Centile vs PSA (ng/ml) from Vickers et al., 2010-- for age 60
Table for Diagnosis(
        [(0,0)-(10,10)],(1,1),(1,1))
Units: 1/Year
Table for Empirical pdf(
        [(0,0)-(10,10)],(0,1),(1,1))
Units: dmnl
"Table ROC for PSA Etzioni et al., 2004"([[(0,0)-(1,1)]],(0,0),(0.0157,0.1363),(0.0283,0.1536),(0.033,0.18181),(0.05,
0.18861),(0.06089,0.2251),(0.065,0.2377),(0.069291,0.258621),(0.0745,0.26907
),(0.08,0.3),(0.086,0.3286),(0.091,0.334),(0.1144,0.3777),(0.127,0.4184),(0.145932
,0.4331),(0.165879,0.447753),(0.186877,0.4686),(0.207874,0.544932),(0.230971
,0.6013),(0.2561,0.644),(0.29186,0.67),(0.341207,0.7476),(0.464042,0.867816
),(0.5238,0.9242),(0.6845,0.9524),(0.86,0.964995),(1,1))
Units: dmnl
Etzioni et al., 2004: http://www.ncbi.nlm.nih.gov/pubmed/15466981 IS THIS EVERYBODY?
"Table ROC for PSA Jacobsen et al., 1996 age 50-59"(
        [(0,0)-(1,1)],(0,0),(0.00186732,0.549412),(0.0110716,0.54945),(0.0132657,0.66469
),(0.0586649,0.829493),(0.0610873,0.884374),(0.22018,0.887773),(0.226558,0.939927
),(0.36836,0.995383),(0.98373,0.999287),(1,1))
Units: dmnl
"Table ROC for PSA Jacobsen et al., 1996 age 60-69"([[(0,0)-
(1,1)]],(0,0),(0.0157,0.1363),(0.0283,0.1536),(0.033,0.18181),(0.05,
0.18861),(0.06089,0.2251),(0.065,0.2377),(0.069291,0.258621),(0.0745,0.26907
),(0.08,0.3),(0.086,0.3286),(0.091,0.334),(0.1144,0.3777),(0.127,0.4184),(0.145932
,0.4331),(0.165879,0.447753),(0.186877,0.4686),(0.207874,0.544932),(0.230971

177

,0.6013),(0.2561,0.644),(0.29186,0.67),(0.341207,0.7476),(0.464042,0.867816
),(0.5238,0.9242),(0.6845,0.9524),(0.86,0.964995),(1,1))
Units: dmnl
"Table ROC for PSA Jacobsen et al., 1996 age 70-79"([(0,0)-
(1,1)],(0,0),(0.00564086,0.594697),(0.011908,0.502127),(0.0278853,0.623596
),(0.0293013,0.596852),(0.0460087,0.69912),(0.0476244,0.619562),(0.0813555,
0.740419),(0.0815059,0.700638),(0.114197,0.748785),(0.114223,0.741926),(0.157552
,0.758566),(0.157573,0.753079),(0.167973,0.784673),(0.170686,0.762736),(0.200586
,0.853397),(0.200841,0.78618),(0.209739,0.867153),(0.212436,0.849331),(0.22543
,0.890538),(0.225497,0.872705),(0.300369,0.89359),(0.333215,0.900584),(0.354192
,0.917132),(0.542135,0.941226),(0.543517,0.923398),(0.5934,0.945552),(0.681478
,0.951402),(0.691956,0.96242),(0.762904,0.977801),(0.762955,0.964084),(0.893095
,0.974222),(0.895621,1),(1,1))
Units: dmnl
"Table ROC for PSA Jacobsen et al., 1996 AUC=0.83"([(0,0)-
(1,1)],(0,0),(0.0152461,0.282504),(0.0248979,0.393864),(0.0444038,0.509368
),(0.10142,0.606392),(0.176304,0.641598),(0.221576,0.691176),(0.266878,0.724258
),(0.339716,0.798635),(0.426388,0.858607),(0.532807,0.906249),(0.641241,0.931215
),(0.74377,0.949983),(0.862089,0.962598),(0.962638,0.985486),(0.994169,0.999984
),(1,1))
Units: dmnl
figure 3. jacobsen et al., 1996- panel B. AUC=0.83. is this D+
                    or overall population?
"Table ROC for PSA, Steuber et al., 2008"([(0,0)-(1,1)],(0,0),(0.0108163,0.0553176),(0.0411861,0.0663138),(0.076929,
0.0911456),(0.0859723,0.190844),(0.132449,0.232267),(0.15043,0.34025),(0.20586
,0.403809),(0.243424,0.459107),(0.259553,0.508924),(0.284652,0.594727),(0.320417
,0.638949),(0.409724,0.658093),(0.440142,0.71064),(0.502702,0.763099),(0.568834
,0.815547),(0.613506,0.840354),(0.613506,0.840354),(0.713521,0.853928),(0.772523
,0.917476),(0.843996,0.95606),(0.927969,0.994608),(1,0.999965))
Units: dmnl
STEUBER ET AL., 2008
"Table ROC for PSA, Thompson et al., 2005 AUC=0.678"([(0,0)-
(1,1)],(0,0),(0.0229244,0.0658477),(0.040774,0.136822),(0.0636109,0.205233
),(0.10396,0.276094),(0.141771,0.339353),(0.176996,0.384858),(0.224782,0.442991
),(0.267606,0.508762),(0.325467,0.582072),(0.39579,0.647704),(0.471076,0.705696
),(0.551436,0.778892),(0.629234,0.83941),(0.812192,0.932388),(0.89734,0.962413
),(1,1))
Units: dmnl
Thompson et al., 2005. Empirical PSA curve: Operating
                    Characteristics of Prostate-Specific Antigen in Men With an
                    Initial PSA Level of 3.0 ng/mL or Lower. JAMA.
                    2005;294(1):66-70. http://www.ncbi.nlm.nih.gov/pubmed/15998892
                    Any PCa vs no PCa (AUC=0.678)
"Table ROC for PSA, Underwood et al. 2012 0"([(0,0)-
(1,1)],(0,0),(0.00745342,0.0697674),(0.0223602,0.132267),(0.0310559
,0.178779),(0.0434783,0.235465),(0.0559006,0.284884),(0.0770186,0.337209),(
0.0956522,0.375),(0.120497,0.422965),(0.146584,0.460756),(0.182609,0.497093
),(0.213665,0.52907),(0.270807,0.579942),(0.330435,0.62936),(0.386335,0.667151
),(0.453416,0.712209),(0.518012,0.752907),(0.573913,0.780523),(0.626087,0.806686
),(0.689441,0.838663),(0.73913,0.861919),(0.8,0.890988),(0.862112,0.917151)
,(0.893168,0.934593),(0.936646,0.954942),(0.971429,0.97093),(1,1))
Units: dmnl
Underwood et al., 2012--data from Zhang et al., 2012. Receiver
                    Operating Characteristic (ROC) curve illustrating the imperfect
                    nature of PSA testing based on longitudinal data for a regional
                    population in Rochester, MN. 1983-2005, N=11.872 men, mean
                    age=63, 95% Caucasian.
                    http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3711512/
"Table ROC for PSA, Underwood et al. 2012 1"([(0,0)-
(1,1)],(0,0),(0.00745342,0.0697674),(0.0223602,0.132267),(0.0310559
,0.178779),(0.0434783,0.235465),(0.0559006,0.284884),(0.0770186,0.337209),(

178

0.0956522,0.375),(0.120497,0.422965),(0.146584,0.460756),(0.182609,0.497093
),(0.213665,0.52907),(0.270807,0.579942),(0.330435,0.62936),(0.386335,0.667151
),(0.453416,0.712209),(0.518012,0.752907),(0.573913,0.780523),(0.626087,0.806686
),(0.689441,0.838663),(0.73913,0.861919),(0.8,0.890988),(0.862112,0.917151)
,(0.893168,0.934593),(0.936646,0.954942),(0.971429,0.97093),(1,1))
Units: dmnl
Underwood et al., 2012--data from Zhang et al., 2012. Receiver
　　　　　　　Operating Characteristic (ROC) curve illustrating the imperfect
　　　　　　　nature of PSA testing based on longitudinal data for a regional
　　　　　　　population in Rochester, MN. 1983-2005, N=11.872 men, mean
　　　　　　　age=63, 95% Caucasian.
"Table ROC for PSA, Underwood et al. 2012"([(0,0)-
(1,1)],(0,0),(0.00745342,0.0697674),(0.0223602,0.132267),(0.0310559
,0.178779),(0.0434783,0.235465),(0.0559006,0.284884),(0.0770186,0.337209),(
0.0956522,0.375),(0.120497,0.422965),(0.146584,0.460756),(0.182609,0.497093
),(0.213665,0.52907),(0.270807,0.579942),(0.330435,0.62936),(0.386335,0.667151
),(0.453416,0.712209),(0.518012,0.752907),(0.573913,0.780523),(0.626087,0.806686
),(0.689441,0.838663),(0.73913,0.861919),(0.8,0.890988),(0.862112,0.917151)
,(0.893168,0.934593),(0.936646,0.954942),(0.971429,0.97093),(1,1))
Units: dmnl
Underwood et al., 2012--data from Zhang et al., 2012. Receiver
"Table ROC for PSA Jacobsen et al., 1996 AUC=0.72"(
　　　　　[(0,0)-(1,1)],(0,0),(0.0143666,0.069692),(0.0300489,0.13802),(0.0470402,0.210448
),(0.0798191,0.26787),(0.123107,0.328038),(0.149354,0.355397),(0.169006,0.401872
),(0.229399,0.444304),(0.253031,0.46073),(0.280566,0.508582),(0.312038,0.560538
),(0.348756,0.620697),(0.413067,0.682261),(0.480018,0.734265),(0.520716,0.764375
),(0.56403,0.804052),(0.604703,0.853288),(0.65063,0.905264),(0.716295,0.935408
),(0.778031,0.954618),(0.818746,0.971067),(0.877869,0.979345),(0.931738,0.984883
),(0.989545,0.994525),(1,1))
Units: dmnl
"Table ROC for PSA, Ahn et al. 2014 AUC=0.577"(
　　　　　[(0,0)-(1,1)],(0,0),(0.0242482,0.0298266),(0.0797644,0.0526511),(0.11618,0.0771904
),(0.135187,0.129671),(0.17157,0.173442),(0.209635,0.248683),(0.232072,0.325646
),(0.273672,0.364181),(0.292691,0.409669),(0.327361,0.43945),(0.355109,0.456981
),(0.368913,0.505957),(0.407017,0.558471),(0.469424,0.612776),(0.521426,0.66007
),(0.556048,0.717823),(0.661842,0.780946),(0.776232,0.893035),(0.84215,0.924619
),(0.887222,0.963159),(0.965317,0.980778),(1,1))
Units: dmnl
ahn et al. 2014 auc=0.577

"Table ROC for PSA, Ferro et al., 2015"(
　　　　　[(0,0)-(1,1)],(0,0),(0.0208271,0.0217948),(0.0464358,0.0559562),(0.0639132
,0.11771),(0.098961,0.213526),(0.127744,0.260034),(0.170995,0.30672),(0.228643
,0.375122),(0.254376,0.372362),(0.27817,0.46804),(0.310158,0.517664),(0.346937
,0.576579),(0.396692,0.601807),(0.444787,0.642399),(0.483195,0.695179),(0.532908
,0.732714),(0.564864,0.791569),(0.651491,0.84802),(0.734944,0.892124),(0.813533
,0.948476),(0.909889,0.980431),(0.982171,0.999782),(1,1))
Units: dmnl
Ferro et al., 2015--AUC= 0.639 (0.592-0.687)
"Table ROC for PSA, Thompson et al., 2005 Gleason>7 or no PCa"(
　　　　　[(0,0)-(1,1)],(0,0),(0.0231494,0.111531),(0.0463238,0.248468),(0.0642109,0.327056
),(0.0995725,0.40048),(0.11996,0.479055
),(0.150284,0.54489),(0.200607,0.610624),(0.246006,0.691611),(0.328817,0.754641
),(0.406577,0.807545),(0.481888,0.870614)
,(0.599573,0.908087),(0.68472,0.938111),(0.722269,0.948073),(0.767268,0.947845
),(0.844916,0.977907),(0.90749,0.992818),(
1,1))
Units: dmnl
Thompson et al., 2005. Empirical PSA curve: Operating
　　　　　　　Characteristics of Prostate-Specific Antigen in Men With an
　　　　　　　Initial PSA Level of 3.0 ng/mL or Lower. JAMA.

2005;294(1):66-70. http://www.ncbi.nlm.nih.gov/pubmed/15998892
Gleason grade>=7 (high grade) vs. Gleason grade<7 (low grade) or
No PCa (AUC=0.782)
"Table ROC for PSA, Thompson et al., 2005 Gleason>8 or no PCa"(
[(0,0)-(1,1)],(0,0),(0.0107372,0.129361),(0.0290493,0.29424),(0.059561,0.398145
),(0.079923,0.471644),(0.11011,0.509562),(0.142796,0.547466),(0.168196,0.628555
),(0.20107,0.704529),(0.253994,0.790554),(0.271756,0.843762),(0.321742,0.840971
),(0.351854,0.86366),(0.406852,0.863381),(0.529762,0.946512),(0.669746,0.943264
),(0.854916,0.977856),(1,1))
Units: dmnl
Thompson et al., 2005.
testoutcome:Tplus,Tminus
Threshold Switching=IF THEN ELSE(Time>Screening Start Year, Switch T , 0)
Units: dmnl
Switch is on if T is allowed to change endogenously, off if set
to be constant. 1986 is the year PSA screening has started.
Threshold T= INTEG (Change in Threshold, INIT Threshold)
Units: dmnl
given in ng/ml. Threshold is the Cutoff value for the Test
Outcome. Values above T will be considered as test positive
(unhealthy), values below T will be considered as test negative
(healthy). There is no specific normal or abnormal level of PSA
in the blood.
Threshold Table([(1975,0)-(2050,10)],(1975,0),(1985,0),(1986,0),(1987,0),(1988,0),(1989,0)
,(1990,4),(1991,4),(1992,4),(1993,4),(1994,4),(1995,4),(1996,4),(1997,4),(1998
,4),(1999,4),(2000,4),(2001,4),(2002,4),(2003,4),(2004,4),(2005,4),(2006,0)
,(2050,0))
Units: dmnl
The standard for biopsy referral in the US from 1990 to 2005 was
a PSA level greater than 4 ng/ml. Gulati et al., 2013. Their
model allows men to get a biosy and diagnosis after screening if
their PSA exceeds this threhold.
TIME STEP = 0.0625
Units: Year [0,?]
The time step for the simulation.
Time to Adj R=1.5
Units: Year
Time constant for change of recommended starting age
Time to Adj T=1.5
Units: Year
Adjustment time constant for the rate of change of the Threshold value T.
TP=1-"CDF of Threshold for D+"
Units: dmnl
True positive fraction
Treatment=1
Units: dmnl
"True Neg Rate (TNR)"=1-"False Pos Rate (FPR)"
Units: dmnl
True negative rate
"True Pos Rate (TPR)"=1-(NCDF((LnEffThreshold-"Mu D+")/(2*"Sigma D+")^0.5))
Units: dmnl
True positive rate, also known as the "True positive fraction".
=P(T+/D+). TPR is defined as the fraction of correctly
classified diseased subjects. In signal detection theory,
overall performance depends both on accuracy (otherwise known as
'sensitivity' or 'TPR') of judgment and on the threshold
(otherwise known as 'bias'). 1-(NCDF((Effective
Threshold-"Mean D+")/(2*"Stdev D+")^0.5))
Unit Benefit[testoutcome,diseasestate]=3,0;0,0.5;
Units: dmnl
Non-negative unit benefits for possible test outcome and disease state pairs 3,0;0,0.5; 6,0;0,0.75;

Unit Cost[testoutcome,diseasestate]=0,1.5;2,0;
Units: dmnl
non-negative unit costs for possible test outcome and disease state pairs 0,1.5;2,0; 0,0.5;1,0;

APPENDIX P: List of Equations for Essay#3

"% D+"=
                        0.3
            Units: dmnl
            Assumption: Prevalence of disease in target screening population
                              D+ is highest among American men of African origin, but trends are
                              similar among all countries reporting. Prevalance were lowest
                              among men of Mediterranean and Asian origin. Prevalence of latent
                              carcinoma: Soos et al., Hungary, Overall, 38.8%; Rebeck et al.,
                              2014. African, Overall, 23% Dhom et al., 1983. Saarland 1978,
                              36% --- Japan, 21.1--Texas and Louisiana, 30.8%--Hawaii, 25.3%--
                              Colombia, 31.3% Breslow et al., 1977-- Israel, 22%, Hong Kong,
                              15%-- Uganda, 24%-- Jamaica, 32%-- Sweden, 40%--Germany,
                              29%--Singapore, 14.4% Yatani et a., 1988- Prevalance increased
                              from 25.6 to 34.6 from 1965-1979 to 1982-1986. but comparable to
                              US whites, 34.6

"1- Percentage Receiving AS"(
        [(1986,0)-(2013,50)],(1986,9.9),(1987,12.4),(1988,15.2),(1991,26.1),(1992,
29.4),(1993,29.2),(2003,38.2),(2004,39.4),(2005,40.4),(2006,42.7),(2007,45.6
),(2008,47.6),(2009,48.2),(2010,49.2),(2011,49.3),(2012,47.8),(2013,47.3)

        {1986-1993 are from Mettlin et al., 1996--NCDB,
         2003-2013 are from GET DATA: http://oliver.facs.org/BMPub/index.cfm by diagnosis year, first course
treatment
         1992: 31.6, 1995: 34.1 Mettlin et al., 1998})
Units: 1/year
Represents Expectant management, conservative management, active
                    surveillance, or watchful waiting. there are slight differences
                    in definition. Active surveillance started in 2010. Before there
                    was no treatment or it used to be called conservative
                    management. GET DATA: http://oliver.facs.org/BMPub/index.cfm by
                    diagnosis year, first course treatment. {1986-1993 are from
                    Mettlin et al., 1996--NCDB, 2003-2013 are from GET DATA:
                    http://oliver.facs.org/BMPub/index.cfm by diagnosis year, first
                    course treatment after 2010 it is called active surveillance,
                    active surveillance rates for 2010: 3.6, 2011: 4.8, 2012: 5.6,
                    2013: 6.6} 1992: 20, 1995: 21.6-- Mettlin et al., 1998} Among
                    men with clinically more aggressive cancers, African Americans
                    are less likely to undergo RP and more likely to undergo CM.
                    (Hoffman et al., 2003, refs 11-13, 29-33). They are also at
                    increased risk for presenting with advanced stage disease (Ries
                    et al., 2002). Racial disparities observed for other types of
                    cancers. refs 38-39.

"2- Percentage Receiving RT"(
        [(1986,0)-(2013,50)],(1986,41.8),(1987,38),(1988,34.6),(1991,25.1),(1992,20.8
),(1993,21.6),(2003,7.1),(2004,7.2),(2005,7.3),(2006,7.2),(2007,7.3),(2008,
8.1),(2009,9.3),(2010,9.4),(2011,10.8),(2012,12.1),(2013,13.5))
Units: 1/year
including brachytherapy. RT rates by clinical satge are 27%,
                    38%, 54%, and 16%, in 1997 (Meltzer et al., 2001). {1986-1993
                    are from Mettlin et al., 1996--NCDB, 2003-2013 are from GET

181

"3- Percentage Receiving RP"(
[(1986,0)-(2013,50)],(1986,26.7),(1987,27.3),(1988,27.7),(1991,28.1),(1992,30.6),(1993,30.1),(2003,22.4),(2004,22.3),(2005,22.4),(2006,22),(2007,21.3),(2008,20.2),(2009,19.2),(2010,18.3),(2011,17.4),(2012,16),(2013,14.7)

{1986-1993 are from Mettlin et al., 1996--NCDB,
2003-2013 are from GET DATA: http://oliver.facs.org/BMPub/index.cfm by diagnosis year, first course treatment}
)
Units: 1/year
Surgery. Men with a Screening Detected Cancer are more likely to
consider aggressive treatment than those with incidental cancers, as evidences by increased rate of RP and RT following the introduction of PSA (Hoffman, 2003, refs 11-13). RP is generally reserved for local stage cancer. In 1997, 37% of stage B and 78% of stage C patients receive RP. Most men younger than 65 years with stage A or B choose surgery, but RP rates fall rapidly after 70 years of age. GET DATA: http://oliver.facs.org/BMPub/index.cfm by diagnosis year, first course treatment. {1986-1993 are from Mettlin et al., 1996--NCDB, {1986-1993 are from Mettlin et al., 1996--NCDB, 2003-2013 are from GET DATA: http://oliver.facs.org/BMPub/index.cfm by diagnosis year, first course treatment 1992: 31.6, 1995: 34.1 Mettlin et al., 1998}

Actual Starting Age for Routine Screening=
SMOOTH3(Effective Recommended Starting Age, Public Perception Delay)
Units: Ages
The actual starting age for routine screening, as affected by
recommendations and advocacy groups

Actual Time Spent in AtRisk=
ZIDZ(SUM(At Risk Never Screened Pop[Age!]),(SUM(AsxInci[Age!,Grade!])+SUM(Initial Screening FP Rate[Age!])+SUM(Initial Screening TN Rate
[Age!])+SUM(XXocAtRisk[Age!])))
Units: year
compare to literature before/ after screening starts in 1987.

Actual Time Spent in AtRiskFP=
ZIDZ(SUM(At Risk and Screened FP[Age!]),(SUM(XXocAtRiskFP[Age!])+SUM(AsxInci3[Age!,Grade!])+SUM(Rescreened and Negative[
Age!])+SUM(Biopsy and Negative Result[Age!])))
Units: year
compare to literature before/ after screening starts in 1987.

Actual Time Spent in AtRiskTN=
ZIDZ(SUM(At Risk and Screened TN[Age!]),(SUM(AsxInci2[Age!,Grade!])+SUM(Screened and FP Rate[Age!])+SUM(XXocAtRiskTN[Age
!])))
Units: year
compare to literature before/ after screening starts in 1987.

Actual Time Spent in CxM0=
ZIDZ(SUM(Cx LocoRegional M0[Age!,Grade!]),(SUM(XXocCxM0[Age!,Grade!])+SUM(XXpcCxM0[Age!,Grade!])+SUM(txCxM0[Age!,Grade!,Treatment!])+SUM(mxCxM0[Age!,Grade!])))
Units: year

Actual Time Spent in CxM1=
        ZIDZ(SUM(Cx Distant M1[Age!,Grade!]),(SUM(XXocCxM1[Age!,Grade!])+SUM(XXpcCxM1
[Age!,Grade!])+SUM(txCxM1[Age!,Grade!,Treatment
        !])))
Units: year
compare to literature before/ after screening starts in 1987.
                should be even less than 0.4-0.3 years?

Actual Time Spent in SxM0=
        ZIDZ(SUM(Sx LocoRegional M0[Age!,Grade!]),(SUM(XXocSxM0[Age!,Grade!])+SUM(
XXpcSxM0[Age!,Grade!])+SUM(txSxM0[Age!,Grade
        !,Treatment!])+SUM(mxSxM0[Age!,Grade!])))
Units: year
subscript by age group. lead times are different for different
                age groups

Actual Time Spent in SxM1=
        ZIDZ(SUM(Sx Distant M1[Age!,Grade!]),(SUM(XXocSxM1[Age!,Grade!])+SUM(XXpcSxM1
[Age!,Grade!])+SUM(txSxM1[Age!,Grade!,Treatment
        !])))
Units: year
compare to literature after screening starts in 1987 didnt exist
                before screening starts

Actual Time Spent in TxCxM0=
        ZIDZ(SUM(Tx CxM0[Age!,Grade!,Treatment!]),(SUM(XXocTxCxM0[Age!,Grade!,Treatment
!])+SUM(XXpcTxCxM0[Age!,Grade!,Treatment
        !])+SUM(mxTxCxM0[Age!,Grade!,Treatment!])))
Units: year

Actual Time Spent in TxCxM0M1=
        ZIDZ(SUM(Tx CxM0M1[Age!,Grade!,Treatment!]),(SUM(XXocTxCxM0M1[Age!,Grade!,
Treatment!])+SUM(XXpcTxCxM0M1[Age!,Grade!,Treatment
        !])+SUM(retxCxM1[Age!,Grade!,Treatment!])))
Units: year

Actual Time Spent in TxCxM1=
        ZIDZ(SUM(Tx CxM1[Age!,Grade!,Treatment!]),(SUM(XXocTxCxM1[Age!,Grade!,Treatment
!])+SUM(XXpcTxCxM1[Age!,Grade!,Treatment!])))
Units: year

Actual Time Spent in TxSxM0=
        ZIDZ(SUM(Tx SxM0[Age!,Grade!,Treatment!]),(SUM(XXocTxSxM0[Age!,Grade!,Treatment
!])+SUM(XXpcTxSxM0[Age!,Grade!,Treatment
        !])+SUM(mxTxSxM0[Age!,Grade!,Treatment!])))
Units: year

Actual Time Spent in TxSxM0M1=
        ZIDZ(SUM(Tx SxM0M1[Age!,Grade!,Treatment!]),(SUM(XXocTxSxM0M1[Age!,Grade!,
Treatment!])+SUM(XXpcTxSxM0M1[Age!,Grade!,Treatment
        !])+SUM(retxSxM1[Age!,Grade!,Treatment!])))
Units: year

Actual Time Spent in TxSxM1=
        ZIDZ(SUM(Tx SxM1[Age!,Grade!,Treatment!]),(SUM(XXocTxSxM1[Age!,Grade!,Treatment
!])+SUM(XXpcTxSxM1[Age!,Grade!,Treatment
        !])))
Units: year

Actual Time Spent in UxM0=
        ZIDZ(SUM(Ux LocoRegional M0[Age!,Grade!]),(SUM(XXocUxM0[Age!,Grade!])+SUM(

XXpcUxM0[Age!,Grade!])+SUM(mxM0[Age!,Grade
        !])+SUM(sxM0[Age!,Grade!])+SUM(cxM0[Age!,Grade!])))
Units: year
The duration of the preclinical stage in the absence of
                screening (a random variable) is termed sojourn time. 13.5 to 15
                years? It represents the potential time from tumor onset to its
                clinical diagnosis. Weibull distribution with mean and shape
                parameter for baseline sojourn time hazard. Sojourn time =
                f(age, secular trend). Estimate and distribution is in Tsodikov
                et al., 2006 a population model of prostate cancer incidence.
                etzioni et al 1998; gulati et al, 2010 page 714-715. sojourn
                time is given by age groups.Lead time, or the amount of time
                that diagnosis is moved forward by the test (Yao and Yao, 2002).
                Lead-time is included as a survival benefit for CISNET models:
                https://resources.cisnet.cancer.gov/registry/glossary/#assumption
                sbenefit-factorsscreeninglead-time Lead times estimates vary
                depending on the methods and definitions, but estimates of 8-12
                years are well founded. Hence, the follow-up period of trials in
                the PSA era must be at least 8-12 years just to get to the
                median point at which cases would have been diagnosed in the
                pre-PSA era. Source, 2015:
                ttp://onlinelibrary.wiley.com/doi/10.1002/ijc.29408/epdf.
                Average lead time estimates can be found in Telesca et al
                Draisma et al estmated higher lead times of 11.6 years for PSA
                screning for men aged 55-75 years.

Actual Time Spent in UxM1=
        ZIDZ(SUM(Ux Distant M1[Age!,Grade!]),(SUM(XXocUxM1[Age!,Grade!])+SUM(XXpcUxM1
[Age!,Grade!])+SUM(cxM1[Age!,Grade!])+SUM(
        sxM1[Age!,Grade!])))
Units: year
compare to literature before/ after screening starts in 1987

Adapted from PSAPC FHCRC Prostate Cancer Model Natural History Screening Clinical Detection
=
        1
Units: dmnl
FHCRC Prostate Cancer Microsimulation (Extension of Etzioni's
                serial PSA Screening Model)--PCSIM model tutorial page 5 CISNET
                model latest version.
                https://resources.cisnet.cancer.gov/registry/packages/psapc-fhcrc
                / The microsimulation generates clinical and disease histories
                for a hypothetical cohort of men over 30. It has 5 modules: 1-
                Natural History (SEER data, US Census Bureau (USCB), and Nat
                Cent for Health Stats (NCHS). Disease histories are generated by
                combining Etzioni's asymptomatic onset study and Cowen's disease
                progression rates (1994). 2-Clinical Diagnosis (Screening trends
                from Mariotto et al) 3-Serial PSA Screening (DRE testing not
                modeled) 4-PSA Growth (Based on Inoue et al. 2004. Prior
                modeling work Oesterling,1993 and Carter,1994) 5-Prostate Cancer
                Survival (SEER survival data)

Adjust dt rate[AgeGroup35to39]=
        1
Adjust dt rate[AgeGroup40to44]=
        1
Adjust dt rate[AgeGroup45to49]=
        1
Adjust dt rate[AgeGroup50to54]=
        1
Adjust dt rate[AgeGroup55to59]=

1
Adjust dt rate[AgeGroup60to64]=
1
Adjust dt rate[AgeGroup65to69]=
1
Adjust dt rate[AgeGroup70to74]=
1
Adjust dt rate[AgeGroup75to79]=
1
Adjust dt rate[AgeGroup80plus]=
0.9
Units: dmnl
Adjustment factor for death rates by decade// unnecessary=1

Adoption Fraction F= INTEG (
AF dot,
0)
Units: dmnl

Adult men counts time series projection millions[AgeGroup35to39]:INTERPOLATE:
:=
Adult men popn counts time series projection[AgeGroup35to39]*1000
Adult men counts time series projection millions[AgeGroup40to44]:INTERPOLATE:
:=
Adult men popn counts time series projection[AgeGroup40to44]*1000
Adult men counts time series projection millions[AgeGroup45to49]:INTERPOLATE:
:=
Adult men popn counts time series projection[AgeGroup45to49]*1000
Adult men counts time series projection millions[AgeGroup50to54]:INTERPOLATE:
:=
Adult men popn counts time series projection[AgeGroup50to54]*1000
Adult men counts time series projection millions[AgeGroup55to59]:INTERPOLATE:
:=
Adult men popn counts time series projection[AgeGroup55to59]*1000
Adult men counts time series projection millions[AgeGroup60to64]:INTERPOLATE:
:=
Adult men popn counts time series projection[AgeGroup60to64]*1000
Adult men counts time series projection millions[AgeGroup65to69]:INTERPOLATE:
:=
Adult men popn counts time series projection[AgeGroup65to69]*1000
Adult men counts time series projection millions[AgeGroup70to74]:INTERPOLATE:
:=
Adult men popn counts time series projection[AgeGroup70to74]*1000
Adult men counts time series projection millions[AgeGroup75to79]:INTERPOLATE:
:=
Adult men popn counts time series projection[AgeGroup75to79]*1000
Adult men counts time series projection millions[AgeGroup80plus]:INTERPOLATE:
:=
Adult men popn counts time series projection[AgeGroup80plus]*1000
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4') Projections: Table
NP2014-T9: Table 9. Projections of the Population by Sex and Age
for the United States: 2015 to 2060 You can certainly get
historical census data by age group. See, for example,
Statistical Abstract of the United States 2012, Table 7;
Resident population by sex and age: 1980 to 2010.

Adult men popn 40to49 data:INTERPOLATE::=
Adult men popn count 40to49*1000
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 40to49:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B58')
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 50minus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B57')
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 50minus data:INTERPOLATE::=
        Adult men popn count 50minus*1000
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 50plus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B56')
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 50plus data:INTERPOLATE::=
        Adult men popn count 50plus*1000
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 50to59:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B59')
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 50to59 data:INTERPOLATE::=
        Adult men popn count 50to59*1000
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 60to69:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B60')
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 60to69 data:INTERPOLATE::=
        Adult men popn count 60to69*1000
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 65minus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B55')
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 65minus data:INTERPOLATE::=
        Adult men popn count 65minus*1000
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 65plus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B54')
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 65plus data:INTERPOLATE::=
        Adult men popn count 65plus*1000
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 70to79:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B61')
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count 70to79 data:INTERPOLATE::=
        Adult men popn count 70to79*1000
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count TOTAL:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B53')

        {Total popn}
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count TOTAL data:INTERPOLATE::=
        Adult men popn count TOTAL*1000
Units: People
GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')

Adult men popn count TOTAL projection:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F53')

        {Total popn}
Units: People

Adult men popn count TOTAL projection millions:INTERPOLATE::=
        Adult men popn count TOTAL projection*1000
Units: People
pop projection 2015 and beyond- table NP2014-T9

Adult men popn counts 0to34:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F121')
Units: People

Adult men popn counts 35to44:=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F103')
Units: People
Future projections 2015 and beyond- Table NP2014-T9

Adult men popn counts 45to54:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F104')
Units: People
Future projections 2015 and beyond- Table NP2014-T9

Adult men popn counts 55to64:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F105')
Units: People
Future projections 2015 and beyond- Table NP2014-T9

Adult men popn counts 65to74:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F106')
Units: People
Future projections 2015 and beyond- Table NP2014-T9

Adult men popn counts 75plus:INTERPOLATE::=
     GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F107')
Units: People
Future projections 2015 and beyond- Table NP2014-T9

Adult men popn counts time series[AgeGroup35to39]:INTERPOLATE::=
     GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B38')
Adult men popn counts time series[AgeGroup40to44]:=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B39')
Adult men popn counts time series[AgeGroup45to49]:=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B40')
Adult men popn counts time series[AgeGroup50to54]:=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B41')
Adult men popn counts time series[AgeGroup55to59]:=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B42')
Adult men popn counts time series[AgeGroup60to64]:=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B43')
Adult men popn counts time series[AgeGroup65to69]:=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B44')
Adult men popn counts time series[AgeGroup70to74]:=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B45')
Adult men popn counts time series[AgeGroup75to79]:=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B46')
Adult men popn counts time series[AgeGroup80plus]:=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B47')
    Units: People
    GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4') Projections: Table
           NP2014-T9: Table 9. Projections of the Population by Sex and Age
           for the United States: 2015 to 2060 You can certainly get
           historical census data by age group. See, for example,
           Statistical Abstract of the United States 2012, Table 7;
           Resident population by sex and age: 1980 to 2010.

Adult men popn counts time series data[AgeGroup35to39]:INTERPOLATE::=
     Adult men popn counts time series[AgeGroup35to39]*1000
Adult men popn counts time series data[AgeGroup40to44]:INTERPOLATE::=
        Adult men popn counts time series[AgeGroup40to44]*1000
Adult men popn counts time series data[AgeGroup45to49]:INTERPOLATE::=
        Adult men popn counts time series[AgeGroup45to49]*1000
Adult men popn counts time series data[AgeGroup50to54]:INTERPOLATE::=
        Adult men popn counts time series[AgeGroup50to54]*1000
Adult men popn counts time series data[AgeGroup55to59]:INTERPOLATE::=
        Adult men popn counts time series[AgeGroup55to59]*1000
Adult men popn counts time series data[AgeGroup60to64]:INTERPOLATE::=
        Adult men popn counts time series[AgeGroup60to64]*1000
Adult men popn counts time series data[AgeGroup65to69]:INTERPOLATE::=
        Adult men popn counts time series[AgeGroup65to69]*1000
Adult men popn counts time series data[AgeGroup70to74]:INTERPOLATE::=
        Adult men popn counts time series[AgeGroup70to74]*1000
Adult men popn counts time series data[AgeGroup75to79]:INTERPOLATE::=
        Adult men popn counts time series[AgeGroup75to79]*1000
Adult men popn counts time series data[AgeGroup80plus]:INTERPOLATE::=
        Adult men popn counts time series[AgeGroup80plus]*1000
    Units: People
    You can certainly get historical census data by age group. See,
           for example, Statistical Abstract of the United States 2012,
           Table 7; Resident population by sex and age: 1980 to 2010.- Jack

Adult men popn counts time series projection[AgeGroup35to39]:INTERPOLATE::=
     GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F38')

Adult men popn counts time series projection[AgeGroup40to44]:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F39')
Adult men popn counts time series projection[AgeGroup45to49]:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F40')
Adult men popn counts time series projection[AgeGroup50to54]:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F41')
Adult men popn counts time series projection[AgeGroup55to59]:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F42')
Adult men popn counts time series projection[AgeGroup60to64]:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F43')
Adult men popn counts time series projection[AgeGroup65to69]:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F44')
Adult men popn counts time series projection[AgeGroup70to74]:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F45')
Adult men popn counts time series projection[AgeGroup75to79]:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F46')
Adult men popn counts time series projection[AgeGroup80plus]:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'F47')
        Units: People
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4') Projections: Table
            NP2014-T9: Table 9. Projections of the Population by Sex and Age
            for the United States: 2015 to 2060 You can certainly get
            historical census data by age group. See, for example,
            Statistical Abstract of the United States 2012, Table 7;
            Resident population by sex and age: 1980 to 2010.

Adult men popn millions initial 1980[Age]=
        6.862e+006,5.708e+006,5.388e+006,5.621e+006,5.482e+006,4.67e+006,3.3785e+006
,3.3785e+006,1.4335e+006,2.1155e+006
Units: People
6.862e+006,5.708e+006,5.388e+006,5.621e+006,5.482e+006,4.67e+006,
            3.3785e+006,3.3785e+006,1.4335e+006,2.1155e+006
            1.25697e+007,1.10089e+007,1.01518e+007,6.7565e+006,3.54841e+006
            Census: Statistical Abstract of the United States 2012, Table 7;
            "resident population by sex and age: 1980 to 2010". 5.1573e+007
            for men under 65, 1.2495e+007 for men above 65
            6.862e+006,5.708e+006,5.388e+006,5.621e+006,5.482e+006,4.67e+006,
            3.3785e+006,3.3785e+006,1.4335e+006,2.1155e+006

Adult men popn millions initial Total=
        SUM(Adult men popn millions initial 1980[Age!])
Units: People

Adult men popn millions turning 35 time series Data:INTERPOLATE::=
        Adult men popn turning 35 time series*1000
Units: People/year
Census: Statistical Abstract of the United States 2012, Table 7;
            "resident population by sex and age: 1980 to 2010". 5.1573e+007
            for men under 65, 1.2495e+007 for men above 65

Adult men popn turning 35 time series:=
        GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B37')
Units: People/year
Census: Statistical Abstract of the United States 2012, Table 7;
            "resident population by sex and age: 1980 to 2010".

Adult Net Immigration=
        SUM(Adult Net Immigration by Age[Age!])
Units: People/year

Adult Net Immigration by Age[Age]=

Imm At Risk[Age]+ImmAtRiskFP[Age]+ImmAtRiskTN[Age]+SUM(ImmCxM0[Age,Grade!]
)+SUM(ImmCxM1[Age,Grade!])+SUM(ImmSxM0[Age,Grade
!])+SUM(ImmSxM1[Age,Grade!])+SUM(ImmTxCxM0[Age,Grade!,Treatment!])+SUM(ImmTxCxM0M1
[Age,Grade!,Treatment!])+SUM(ImmTxCxM1
[Age,Grade!,Treatment!])+SUM(ImmTxSxM0[Age,Grade!,Treatment!])+SUM(ImmTxSxM0M1
[Age,Grade!,Treatment!])+SUM(ImmTxSxM1[Age
,Grade!,Treatment!])+SUM(ImmUxM0[Age,Grade!])+SUM(ImmUxM1[Age,Grade!])
Units: People/year

Adult net immigration rate series(
        [(1980,0)-(2040,0.01)],(1980,0.001),(1985,0.001),(1990,0.001),(1995,0.0015
),(2000,0.0022),(2010,0.0039),(2020,0.0043),(2030,0.0047),(2040,0.0049))
Units: 1/year
Census past and projection\!\!\! from PRISM model. Immigration
                (migration to a country) is one component of interna-tional
                migration; the other component is emigration (migration from a
                country). In its simplest form, international migra-tion is
                defined as any movement across a national border. In the United
                States, federal statistics on international migration are
                produced primarily by the U.S. Census Bureau and the Office of
                Immigra-tion Statistics of the U.S. Department of Homeland
                Security (DHS).The Census Bureau collects data used to estimate
                international migration through its decennial censuses and
                numerous surveys of the U.S. population. The Office of
                Immigration Statistics pub-lishes immigration data in annual
                flow reports and the Yearbook of Immigration Statistics.
                chrome-extension://oemmndcbldboiebfnladdacbdfmadadm/https://www.c
                ensus.gov/prod/2011pubs/12statab/pop.pdf

Advanced frac of true cases initial=
        0.2
Units: dmnl

AF dot=
        IF THEN ELSE(Adoption Fraction F<Max Adoption Fraction,(alpha+beta*Adoption Fraction F
*(Max Adoption Fraction-Adoption Fraction F))*Screen On, 0)
Units: 1/year

Affected Population=
        Cancer survivors*Fraction Experiencing Harms
Units: People

Age:
        Age35to39,AgeGroup40to49,AgeGroup50to59,AgeGroup60to69,AgeGroup70to79,Age80Plus

Age Adjusted Incidence=
        1
Units: 1/year
SEER 9 (1975-2012) ALL stages:
                http://seer.cancer.gov/faststats/selections.php?run=runit&output=
                1&data=1&statistic=1&year=201501&race=1&sex=2&age=1&series=cancer
                &cancer=66

Age Cohort=
        Init Age in Years+Time-1980
Units: year

age distr Ux[Age]=
        0,0,0,0.1,0.2,0.2,0.2,0.1,0.1,0.1
Units: dmnl

"Age Specific Prevalence D+"=
	Min(1,Max(0,(Actual Starting Age for Routine Screening-Baseline Age)*"Slope D+"
+"Baseline D+"))
Units: dmnl
"Baseline D+"+(Actual Starting Age for Routine
	Screening-Baseline Age)*"Slope D+" Age-specific prevalance of
	"histological"(not clinical) PCa, prevalance is plotted as a
	function of host age (time). Prevalence is the number of cases
	of a particular condition that exists in a given population and
	consists of diagnosed cases plus those cases that are present
	but yet undetected. This variable gives the PCa prevalence in
	the screened male population. Prevalance increases with age.
	Jahn et al., 2015, Welch paper 2005. Assumption: Underlying
	disease burden is stable over time. Assumption may not be true
	since race ratios are changing, as well as worldwide trends.

"Age vs D+ Carter, 1990 Japan"=
	"Table Age vs D+ Carter, 1990 Japan Histological"(age2)
Units: dmnl

"Age vs D+ Carter, 1990 US Male Clinical"=
	"Table Age vs D+ Carter, 1990 US Male Clinical"(age2)
Units: dmnl

"Age vs D+ Carter, 1990 US Male"=
	"Table Age vs D+ Carter, 1990 US Histological"(age2)
Units: dmnl

"Age vs D+ Guileyardo, 1980 US Blacks"=
	"Table Age vs D+ Guileyardo, 1980 US Blacks"(age2)
Units: dmnl

"Age vs D+ Guileyardo, 1980 US Whites"=
	"Table Age vs D+ Guileyardo, 1980 US Whites"(age2)
Units: dmnl

"Age vs D+ Haas et al., 2007-all PCa"=
	"Table Age vs D+ Haas et al., 2007-all PCa"(age2)
Units: dmnl

"Age vs D+ Haas et al., 2007-clinically significant"=
	"Table Age vs D+ Haas et al., 2007-clinically significant"(age2)
Units: dmnl

"Age vs D+ Jahn et al., 2015 Asian"=
	"Table Age vs D+ Jahn et al., 2015 Asian"(age2)
Units: dmnl

"Age vs D+ Jahn et al., 2015 US Black"=
	"Table Age vs D+ Jahn et al., 2015 US Black"(age2)
Units: dmnl

"Age vs D+ Jahn et al., 2015 US White-European"=
	"Table Age vs D+ Jahn et al., 2015 US White-European"(age2)
Units: dmnl

"Age vs D+ Rebbeck et al., 2014 African Descent"=
	"Table Age vs D+ Rebbeck et al., 2014 African Descent"(age2)
Units: dmnl

"Age vs D+ Rebbeck et al., 2014 Asian Descent"=

191

"Table Age vs D+ Rebbeck et al., 2014 Asian Descent"(age2)
Units: dmnl

"Age vs D+ Rebbeck et al., 2014 European Descent"=
        "Table Age vs D+ Rebbeck et al., 2014 European Descent"(age2)
Units: dmnl

"Age vs D+ Sakr et al., 1993 US White"=
        "Table Age vs D+ Sakr et al., 1993 US White"(age2)
Units: dmnl

"Age vs D+ Sakr et al., 1993. US Black"=
        "Table Age vs D+ Sakr et al., 1993. US Black"(age2)
Units: dmnl

"Age vs D+ Sakr et al., 1994 African American"=
        "Table Age vs D+ Sakr et al., 1994 African American"(age2)
Units: dmnl

"Age vs D+ Sakr et al., 1994 Caucasian American"=
        "Table Age vs D+ Sakr et al., 1994 Caucasian American"(age2)
Units: dmnl

"Age vs D+ Soos et al., 2005. Hungary"=
        "Table Age vs D+ Soos et al., 2005. Hungary"(age2)
Units: dmnl

"Age vs D+ Stamatiou, 2006. Greece"=
        "Table Age vs D+ Stamatiou, 2006. Greece"(age2)
Units: dmnl

"Age vs D+ Yao, 2002. Spain"=
        "Table Age vs D+ Sanchez-Chapado et al., 2003. Spain"(age2)
Units: dmnl

"Age vs D+ Yatani et al., 1988 Japan 1965-1979"=
        "Table Age vs D+ Yatani et al., 1988 Japan 1965-1979"(age2)
Units: dmnl
One study reported an increase in the frequency of latent
                cancers between two time perios for the same location (Haas et
                al., 2008-ref 19)

"Age vs D+ Yatani et al., 1988 Japan 1982-1986"=
        "Table Age vs D+ Yatani et al., 1988 Japan 1982-1986"(age2)
Units: dmnl

Age vs Prevalence Model=
        Min(1,Max(0,"Baseline D+"+(Time-INITIAL TIME)*"Slope D+"*age year convert)
)
Units: dmnl
Sanchez chapado et al/, 2003--slope for AA and CA, african
                american and caucasian americans is 1.38. R2==0.96, for CM 0.75.
                Fig. 3. Comparison of the prevalence of CaP in Caucasian
                Mediterranean (CM) men, Caucasian-American (CA) men, and
                African-American(AA)men

age year convert=
        1
Units: Ages/year

"Age-adjusted deaths per 100thou Time Series Over 65":INTERPOLATE::=

GET XLS DATA('PSA.xlsx','Sheet1','2', 'G25')
Units: People/year

"Age-adjusted deaths per 100thou Time Series":=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G22')
Units: People/year
Male age-adjusted central death rates per 100000: (ALL AGES!)
                DONT USE THIS?
                https://www.ssa.gov/oact/NOTES/as120/LifeTables_Tbl_1.html#wp1229
                200, and for males:
                https://www.ssa.gov/oact/NOTES/as120/LifeTables_Tbl_4a.html#wp100
                5233, projections till 2100

"Age-adjusted deaths per 100thouTime Series Under 65":INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G24')
Units: People/year
The other thing you should do is to check your deaths against
                Vital Statistics historical deaths for each age group. Here are
                tables for 1999-2007:
                http://www.cdc.gov/nchs/nvss/mortality/gmwk310.htm
                https://www.ssa.gov/oact/NOTES/as120/LifeTables_Tbl_1.html#wp1229
                200

Age10yearcohorts:
        Age35to39,AgeGroup40to49,AgeGroup50to59,AgeGroup60to69,AgeGroup70to79,Age80Plus

age2=
        25+(Time-INITIAL TIME)/nr of years
Units: dmnl
Constant+(Time-INITIAL TIME)/divide by this nr of years

Age35to39:
        AgeGroup35to39

Age50Plus:
        AgeGroup50to54,AgeGroup55to59,AgeGroup60to64,AgeGroup65to69,AgeGroup70to74
,AgeGroup75to79,AgeGroup80plus

Age65Plus:
        AgeGroup65to69,AgeGroup70to74,AgeGroup75to79,AgeGroup80plus

Age80Plus:
        AgeGroup80plus

AgeGpMean[Age]=
        37.5,42.5,47.5,52.5,57.5,62.5,67.5,72.5,77.5,87.5
Units: Ages
years old threshold mean, mean age for 80+ group is taken as 85.
                37.5,42.5,47.5,52.5,57.5,62.5,67.5,72.5,77.5,87

AgeGpStart[Age]=
        35,40,45,50,55,60,65,70,75,80
Units: dmnl

AgeGroup35to44:
        AgeGroup35to39,AgeGroup40to44

AgeGroup40to49:
        AgeGroup40to44,AgeGroup45to49

AgeGroup45to54:

AgeGroup45to49,AgeGroup50to54

AgeGroup50to59:
AgeGroup50to54,AgeGroup55to59

AgeGroup50to65:
AgeGroup50to54,AgeGroup55to59,AgeGroup60to64

AgeGroup55to64:
AgeGroup55to59,AgeGroup60to64

AgeGroup60to69:
AgeGroup60to64,AgeGroup65to69

AgeGroup65to74:
AgeGroup65to69,AgeGroup70to74

AgeGroup65to80:
AgeGroup65to69,AgeGroup70to74,AgeGroup75to79

AgeGroup70to79:
AgeGroup70to74,AgeGroup75to79

AgeGroup75plus:
AgeGroup75to79,AgeGroup80plus

AgeUnder50:
AgeGroup35to39,AgeGroup40to44,AgeGroup45to49

AgeUnder65:
AgeGroup35to39,AgeGroup40to44,AgeGroup45to49,AgeGroup50to54,AgeGroup55to59
,AgeGroup60to64

AgeUnder80:
AgeGroup35to39,AgeGroup40to44,AgeGroup45to49,AgeGroup50to54,AgeGroup55to59
,AgeGroup60to64,AgeGroup65to69,AgeGroup70to74,AgeGroup75to79

Aging Switch=
	1
Units: dmnl

All Cancer Deaths Data=
	1
Units: dmnl
http://seer.cancer.gov/canstat/animator/#y=2013f;o=0011633;v1=010
	000.4FF0000.20.11

All cause Death Rate US=
	1
Units: 1/year
Based on sex-age-specific Census and Vital Stats.

alpha=
	0.025
Units: 1/year [0,0.02,0.001]
0.017 0.02

Alpha HBR=
	0.4
Units: dmnl

Annual Mortality PCa by Age[Age]=
        XXpcbyAge[Age]/Total Popn by age[Age]
Units: 1/year
Etzioni et al., 1999- Table 1.
                http://www.ncbi.nlm.nih.gov/pubmed/10458357 Cowen et al. 1993.
                Table 1. columns 4 and 6

Annual Mortality PCa by Age DATA[AgeGroup35to39]=
        0
Annual Mortality PCa by Age DATA[AgeGroup40to44]=
        2e-006
Annual Mortality PCa by Age DATA[AgeGroup45to49]=
        8e-006
Annual Mortality PCa by Age DATA[AgeGroup50to54]=
        3.6e-005
Annual Mortality PCa by Age DATA[AgeGroup55to59]=
        0.000116
Annual Mortality PCa by Age DATA[AgeGroup60to64]=
        0.000312
Annual Mortality PCa by Age DATA[AgeGroup65to69]=
        0.000712
Annual Mortality PCa by Age DATA[AgeGroup70to74]=
        0.001392
Annual Mortality PCa by Age DATA[AgeGroup75to79]=
        0.00246
Annual Mortality PCa by Age DATA[AgeGroup80plus]=
                (0.004085+0.006168)/2
        Units: dmnl
        Etzioni et al., 1999- Table 1.
                http://www.ncbi.nlm.nih.gov/pubmed/10458357 age groups 80-84 and
                85+ is given seperately

Annual Probability of Having a Test=
        1
Units: 1/year
Screening Dissemination: Annual Probability of Having a Test

Annual Probability of Initial Treatment Choice=
        1
Units: 1/year
Treatment Dissemination: Annual Probability of Initial Treatment
                Choice

Annual Utility Decrement after Metastasis=
        0.24
Units: Utility/(year*person)
Underwood et al., 2012: Simulation optimization of PSA-threshold
                based prostate cancer screening policies.
                http://www.ncbi.nlm.nih.gov/pubmed/22302420 Bremner et al. 2007.
                Med. Dec. Mak. A review and meta-analysis of prostate cancer
                utilities. http://www.ncbi.nlm.nih.gov/pubmed/17502448

Annual Utility Decrement of Living With Treatment before Metastasis=
        0.07
Units: dmnl
Underwood et al., 2012: Simulation optimization of PSA-threshold
                based prostate cancer screening policies..
                http://www.ncbi.nlm.nih.gov/pubmed/22302420 Bremner et al.,
                2007. Med. Dec. Mak. A review and meta-analysis of prostate
                cancer utilities. http://www.ncbi.nlm.nih.gov/pubmed/17502448.

195

arg normal=
          ax/((1+bx^2)^0.5)
Units: dmnl

AsxInci[Age,Grade]=
          At Risk Never Screened Pop[Age]*HazardAsxOnset[Age]*P tumor grade at onset POx
[Grade]
Units: People/year
=At Risk Never Screened Pop*HazardAsxOnset*P tumor low grade at
                    onset pOx1. add subscript by grade, or probability men who
                    develop disease, before getting any screenings. nonadopters?
                    they all develop disease?

AsxInci2[Age,Grade]=
          At Risk and Screened TN[Age]*HazardAsxOnset[Age]*P tumor grade at onset POx
[Grade]
Units: People/year

AsxInci3[Age,Grade]=
          At Risk and Screened FP[Age]*HazardAsxOnset[Age]*P tumor grade at onset POx
[Grade]
Units: People/year

At Risk and Screened FP[Age]= INTEG (
          Initial Screening FP Rate[Age]+Screened and FP Rate[Age]-SUM(AsxInci3[Age,
Grade!])-Biopsy and Negative Result[Age]-Rescreened and Negative
          [Age]-XXocAtRiskFP[Age]+EnterAgeFP[Age]-LeaveAgeFP[Age]+ImmAtRiskFP[Age],
                    0)
Units: People
initial value is zero, no screening at the start of the
                    simulation

At Risk and Screened TN[Age]= INTEG (
          Biopsy and Negative Result[Age]+Initial Screening TN Rate[Age]+Rescreened and Negative
[Age]-SUM(AsxInci2[Age,Grade!])-Screened and FP Rate
          [Age]-XXocAtRiskTN[Age]+EnterAgeTN[Age]-LeaveAgeTN[Age]+ImmAtRiskTN[Age],
                    0)
Units: People
initial value is zero, no screening at the start of the
                    simulation

At Risk Never Screened Pop[Age]= INTEG (
          Male Pop Turning 35[Age]-SUM(AsxInci[Age,Grade!])-Initial Screening FP Rate
[Age]-Initial Screening TN Rate[Age]-XXocAtRisk
          [Age]-LeaveAge[Age]+EnterAge[Age]+Imm At Risk[Age],
                    Adult men popn millions initial 1980[Age]*(1-Init Fract Dplus[Age]))
Units: People
General population, or at risk population, by age group. initial
                    number matters.

AtRisk OC Death Rate=
          XXocAtRisk Total/Total At Risk Popn
Units: 1/year

AtRisk OC Death Rate by Age[Age]=
          ZIDZ(XXocTotalAtRisk by Age[Age],Total At Risk Popn by age[Age])
Units: 1/year

Attribution Bias=
          0.1
Units: dmnl

196

Attribution Bias: incorrect labeling of death from other causes
as death from PCa (Feuer et al., JNCI, 1999).this may have
played a role in the greatly increased PCa deaths in the 1990's.
In 1990's both the PCa incidence and deaths increased. e.g. 0.1
means 10% of o/c death is reclassified as PCa deaths.

AUC= INTEG (
        Change in AUC,
                0)
Units: dmnl
Area Under the Curve. AUC is interpreted as the average value of
sensitivity for all possible values of specificity, is a measure
of the overall performance of a diagnostic test. AUC can take on
any value between 0 and 1, where a bigger value suggests the
better overall performance of a diagnostic test. 1 represents a
perfect test, 0.5 represents a flip coin, a test that is useless
for seperation. Test if this gives 0.5 when means and std's for
D+ and D- are the same. YES it does. This value can be
interpreted as follows (Zhou, Abuchowski & McClish, 2002): 1)
The average value of sensitivity for all possible values of
specificity; 2) The average value of specificity for all
possible values of of sensitivity; 3) The probability that a
randomly selected individual from the positive group has a test
result indicating greater suspicion than that for a randomly
chosen individual from the negative group. When the variable
under study cannot distinguish between the two groups, i.e.
where there is no difference between the two distributions, the
area will be equal to 0.5 (the ROC curve will coincide with the
diagonal). When there is a perfect separation of the values of
the two groups, i.e. there no overlapping of the distributions,
the area under the ROC curve equals 1 (the ROC curve will reach
the upper left corner of the plot).

Average Annual Percentage Reduction=
        1
Units: dmnl
https://www.ssa.gov/oact/NOTES/as120/LifeTables_Tbl_5.html#wp1012
                577

Avg fraction of men screened this year[Age]=
        Current Screened Fraction[Age]/TimeBtwSx
Units: 1/year

Avg Price Per HRT=
        100
Units: $/procedure
Table for Price Per HRT(Time)

Avg Screened Fraction Data[AgeGroup40to44]:=
        GET XLS DATA('PSA.xlsx','EligibleFract','13', 'B14')
Avg Screened Fraction Data[AgeGroup45to49]:=
                GET XLS DATA('PSA.xlsx','EligibleFract','13', 'B15')
Avg Screened Fraction Data[AgeGroup50to54]:=
                GET XLS DATA('PSA.xlsx','EligibleFract','13', 'B16')
Avg Screened Fraction Data[AgeGroup55to59]:=
                GET XLS DATA('PSA.xlsx','EligibleFract','13', 'B17')
Avg Screened Fraction Data[AgeGroup60to64]:=
                GET XLS DATA('PSA.xlsx','EligibleFract','13', 'B18')
Avg Screened Fraction Data[AgeGroup65to69]:=
                GET XLS DATA('PSA.xlsx','EligibleFract','13', 'B19')
Avg Screened Fraction Data[AgeGroup70to74]:=

GET XLS DATA('PSA.xlsx','EligibleFract','13', 'B20')
Avg Screened Fraction Data[AgeGroup75to79]:=
                    GET XLS DATA('PSA.xlsx','EligibleFract','13', 'B21')
Avg Screened Fraction Data[AgeGroup80plus]:=
                    GET XLS DATA('PSA.xlsx','EligibleFract','13', 'B24')
        Units: dmnl

AvgBiopsyThreshold=
        2.5
Units: dmnl

AvgStartingAgetoScreen:INTERPOLATE::=
        50
Units: Ages
Actual starting age is an endogeneous model variable.
                    "Recommended starting age to screen" is a stock variable with 2
                    subscripts representing guideline issuing organizations. 50. GET
                    XLS DATA('PSA.xlsx','EligibleFract','38', 'G39')

AvgTimetoVisit=
        2
Units: year

ax=
        ("Mu D+"-"Mu D-")/"Sigma D+"
Units: dmnl

Base Cost Continuing Per Year=
        3201
Units: $/(year*person)

Base Last Year of Life Cost PCa Death=
        62242
Units: $/person

Base One Time Treatment Cost=
        1910
Units: $/person
subscript by treatment type?

Base Rate=
        1
Units: 1/year
Annual incidence of breast cancer is 0.001 to 0.006, depending
                    on age and other factors (Ries et al., 2003). Annual incidence
                    of prostate cancer is??

Baseline Age=
        30
Units: Ages
Estimates in the literature usually starts for age 30+--Etzioni
                    FHCRC model PSA growth intercept= age 35 35

"Baseline D+"=
        0
Units: dmnl
Baseline prevalance of PCa for men at age 25 (OR BASELINE AGE).
                    Changes between 1-8% for men in their 20-30's, based on race
                    (Jahn et al., 2015, Markov model assumptions, 1994). Previous
                    equation:Table for Effect of Age on D+(Actual Starting Age for
                    Routine Screening) 0.04

Baseline PCa Survival in Absence of Treatment=
          1
Units: dmnl
Baseline PCa Survival in absence of Treatment

BENEFITS[group]=
          SUM(Unit Benefit[group,testoutcome!,diseasestate!]*Probability of Test Outcome
[testoutcome!,diseasestate!])
Units: dmnl
Total amount of benefits for screening

beta=
          0.57
Units: 1/year [0.2,0.8,0.005]
unit 1/year? 0.53 0.57

BiopCompM0=
          0.5

          {may be subscripted by age (65+ vs 65-), biopsy compliance decreases by age. ref from Etzioni et al. important
parameter}
Units: dmnl
andriole and others (2005) report that 44% of men who underwent
                    subsequent biopsy were diagnosed with the disease in the initial
                    screening round. supplementary material of:
                    http://www.ncbi.nlm.nih.gov/pubmed/20530126 AgeUnder65=0.5,
                    Age65Plus=0.3 --Men who test positive undergo biopsy with
                    specified probabilities that vary with PSA level based on
                    biopsy frequencies--PLCO Trial: 40% for PSA between 4 and 7, 53%
                    for PSA between 7 and 10, and 69% for PSA greater than 10 (ref
                    21 of Etzioni et al., 2008). 0.4 on average in the US. Biopsy
                    uptake. Lane et al., Lancet. 2014: 0.32 for the US, 0.84 for
                    Europe. tends to decrease by age, increase by disease stage.
                    Biopsy frequency for men with PSA between 2-4 ng/ml is taken as
                    the same as that for men with a PSA between 4-7 ng/ml.
                    approximately 40% (Pinsky and others, 2005) from Gulati et al.,
                    2010. Calibrating disease progression paper. 0.4 for the US, 0.9
                    for Europe.. compliance with biopsy referral depends on age and
                    PSA level as observed in the PLCO cancer screening trial, and
                    biopsy sensitivity increases with the dissemination of extended
                    biopsy schemes over time. The MISCAN-PRO and SCANS models
                    estimate an effective test sensitivity which combines the
                    probability of a positive PSA test, receipt of biopsy, and
                    sensitivity of the biopsy to detect latent cancer.
                    https://resources.cisnet.cancer.gov/registry/site-summary/prostat
                    e/ Not all men with a positive PSA test result will submit to a
                    follow-up biopsy. The model assumes that the biopsy rate
                    following a positive PSA test is similar to the one year biopsy
                    frequencies presented in Pinsky et al (PCSIM page 11)
                    http://www.ncbi.nlm.nih.gov/pubmed/15711261

BiopCompM1=
          0.9
Units: dmnl
0.4 for the US, 0.9 for Europe.. compliance with biopsy referral
                    depends on age and PSA level as observed in the PLCO cancer
                    screening trial, and biopsy sensitivity increases with the
                    dissemination of extended biopsy schemes over time. Our
                    model--like the MISCAN-PRO and SCANS models--- estimates an
                    effective test sensitivity which combines the probability of a

positive PSA test, receipt of biopsy, and sensitivity of the
biopsy to detect latent cancer.
https://resources.cisnet.cancer.gov/registry/site-summary/prostat
e/

BiopDetectM0=
Table for Biopsy Detection(Time)
Units: dmnl
Biopsy detection rate for patients with PCa. Underwood et al.,
2012- Table 3. Each biopsy is associated with a sensitivity that
increases over time following trends in the United States toward
more biopsy protocols. 6-core biopsies missed 20-30% of cancers.
(Etzioni et al., 2008). Biopsy detection rate before metastasis,
in the local-regional stage (M0). Haas et al, 2007 estimate that
the PCa detection rate for prostate biopy is 0.8--2007. for an
18 core biopsy regimen.sextant biopsies miss more than 70% of
pca. 12 cores, reaches 80% Underwood et al., 2012--defined as
biopsy detection rate for patients with PCa, f. Haas et al. [31]
estimate that the prostate cancer detection rate for prostate
biopsy is about 0.8. For a detailed discussion of prostate
biopsy standards, see Djavan and Margreiter [17].

BiopDetectM1=
1
Units: dmnl
Biopsy detection rate after metastasis, take as 1. After
metastasis disease is almost always detected by biopsy. We
assume that biopsy is 100% accurate when disease progressed
beytond stage M0 (PCSIM page 11)

Biopsy Accuracy Rate=
1
Units: dmnl
Biopsy Accuracy Rate; or the probability that a biopsy will
detect a tumor if it is present, increases across calendar years
mainly due to increased number of cores taken for biopsy (6 to
12, saturated biopsy is 36 samples). Biopsy accuracy increases
to 100% for individuals within n years of transitioning to M1
metastatic disease. PAGE 18--Biopsy sensitivity increases
linearly with the number or cores taken. Biopsy schemes have
changed over time period.

Biopsy and Negative Result[Age]=
At Risk and Screened FP[Age]/TimetoRecall*BiopCompM0
Units: People/year
If it is D-, biopsy cannot find any disease with 100-, so
(1-BiopDetectM0) is removed from equation

Biopsy Compliance Rate=
0.4
Units: dmnl
Biopsy compliance rate; or the probability a biopsy is performed
﹔   if referred (frequencies may depend on PSA level and age, or
stage). page 18 figure. mean around 0.4-0.5, decreases by age,
increases by PSA result. Biopsy compliance increases to 100% for
individuals within n years of transitioning to M1 metastatic
disease.

Biopsy Rate by age[Age]=
Biopsy Rate PSA FP[Age]+SUM(Biopsy Rate PSA M0Low[Age,Grade!])+SUM(Biopsy Rate PSA M1Low
[Age,Grade!])+SUM(Biopsy Rate CxM0Low[Age,Grade!])+SUM(Biopsy Rate CxM1Low[

Age,Grade!])
Units: Biopsies/year

Biopsy Rate CxM0Low[Age,Grade]=
        cxM0[Age,Grade]*Number of Biopsies Per Dplus Case
Units: Biopsies/year

Biopsy Rate CxM1Low[Age,Grade]=
        Number of Biopsies Per Dplus Case*cxM1[Age,Grade]
Units: Biopsies/year

Biopsy Rate PSA FP[Age]=
        At Risk and Screened FP[Age]/TimetoRecall*BiopCompM0*Number of Biopsies Per FP Case
Units: Biopsies/year
biopsies per year, of people who receive a biopsy to rule out
                cancer. 100% of them are negative so result has to come out
                negative.

Biopsy Rate PSA Indolent[Age,Grade]=
        Ux M0 Ind*SensM0*BiopCompM0/TimeBtwSx*Number of Biopsies Per Dplus Case
Units: Biopsies/year

Biopsy Rate PSA M0Low[Age,Grade]=
        Ux LocoRegional M0[Age,Grade]/TimeBtwSx*SensM0*BiopCompM0*Number of Biopsies Per Dplus Case
Units: Biopsies/year

Biopsy Rate PSA M1Low[Age,Grade]=
        Ux Distant M1[Age,Grade]/TimeBtwSx*SensM1*BiopCompM1*Number of Biopsies Per Dplus Case
Units: Biopsies/year

Biopsy Sensitivity Rate by Calendar Year=
        Table for Biopsy Sensitivity(Time)
Units: dmnl
page 19- 6 core sensitivity is 80% sensitive, 8+ cores are 100%
                sensitive, the proportion of 6-core scemens increase linearly
                after 1995 in favor of 8+ cores. biopsy sensitivity to be forced
                to 100% within n=2 years after transitioning to M1 metastatic
                disease.

bx=
        "Sigma D-"/"Sigma D+"
Units: dmnl

Calculated Total Popn= INTEG (
        SUM(Pop Increase2[Age!])-Total death rate,
                SUM(Adult men popn millions initial 1980[Age!]))
Units: People
check mass balance

Cancer Prevelance and Cost of Care Projections=
        1
Units: dmnl
http://costprojections.cancer.gov/ or
                http://costprojections.cancer.gov/expenditures.html Mariotto AB,
                Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the Cost
                of Cancer Care in the U.S.: 2010-2020. J Natl Cancer Inst. 2011
                Jan. http://jnci.oxfordjournals.org/content/103/2/117.long
                http://costprojections.cancer.gov/expenditures.html
                http://costprojections.cancer.gov/graph.php
                http://costprojections.cancer.gov/annual.costs.html

"Cancer statistics, 2015"=
        1
Units: dmnl
Jemal et al., 2015.
                http://onlinelibrary.wiley.com/doi/10.3322/caac.21254/full

Cancer Survivor Rates=
        100
Units: People
Today, more people are likely to know a cancer survivor than
                before. Between 1971 and 2007, the number of cancer survivors
                more than doubles, from 1.5% to 4% of the population. (CDC.
                Cancer survivors: United States, 2007..2011). A 4 month sample
                of 18 daily newspapers and magazines in 2005 found that, on
                average, each periodical published a new cancer survivor story
                at least once a month (Kromm et al., J Cancer Surviv. 2007).

Cancer survivors=
                Nr Treated by treatment[RadioTheraphy]+Nr Treated by treatment[RadicalProstatectomy
]
Units: People
Nr Treated with Primary Treatment

Cancer Survivors Data:INTERPOLATE::=
                GET XLS DATA('PSA.xlsx','Sheet1','2', 'G9')
Units: 1/year
Cancer survivor: any person diagnosed with cancer, from the time
                of initial diagnosis until his or her death.
                https://costprojections.cancer.gov/graph.php#

"CDF D+ Jacobsen 1996, 50-59"=
                "Table D+ for CDF Jacobsen 1996, 50-59"(Cutoff X)/100
Units: dmnl

"CDF D+ Jacobsen 1996, 60-79"=
                "Table D+ for CDF Jacobsen 1996, 60-79"(Cutoff X)/100
Units: dmnl

"CDF D+ Porter et al., 2006 men 60+"=
                "Table D+ for CDF Porter et al., 2006 men 60+"(Cutoff X)
Units: dmnl

"CDF D+ Zhang et al., 2012"=
                "Table D+ for CDF Zhang et al., 2012"(Cutoff X)
Units: dmnl

"CDF D- Jacobsen 1996, 50-59"=
                "Table D- for CDF Jacobsen 1996, 50-59"(Cutoff X)/100
Units: dmnl

"CDF D- Jacobsen 1996, 60-69"=
                "Table D- for CDF Jacobsen 1996, 60-69"(Cutoff X)/100
Units: dmnl

"CDF D- Jacobsen 1996, 70-79"=
                "Table D- for CDF Jacobsen 1996, 70-79"(Cutoff X)/100
Units: dmnl

"CDF D- Porter et al., 2006 men 40-49"=
                "Table D- for CDF Porter et al., 2006 men 40-49"(Cutoff X)/100
Units: dmnl

"CDF D- Porter et al., 2006 men 60-69"=
        "Table D- for CDF Porter et al., 2006 men 60-69"(Cutoff X)/100
Units: dmnl

"CDF D- Porter et al., 2006 men 70-79"=
        "Table D- for CDF Porter et al., 2006 men 70-79"(Cutoff X)/100
Units: dmnl

"CDF D- Zhang et al., 2012"=
        "Table D- for CDF Zhang et al., 2012"(Cutoff X)
Units: dmnl

CDF of T=
        "CDF of Threshold for D+"*"% D+"+"CDF of Threshold for D-"*(1-"% D+")
Units: dmnl

"CDF of Threshold for D+"=
        (NCDF((LnX-"Mu D+")/(2*"Sigma D+")^0.5))
Units: dmnl
Cumulative density of the D+ distribution at cutoff point
                C--LOGNORMAL.

"CDF of Threshold for D-"=
        (NCDF((LnX-"Mu D-")/(2*"Sigma D-")^0.5))
Units: dmnl
Cumulative density of the D- distribution at cutoff point
                C--LOGNORMAL.

"CDF Vickers et al. 2010"=
        "Table for CDF Vickers et al. 2010"(Cutoff X)/100
Units: dmnl

Census Data=
        1
Units: dmnl
http://factfinder.census.gov/faces/nav/jsf/pages/index.xhtml
                https://www.census.gov/popest/data/index.html
                https://www.census.gov/topics/population/age-and-sex.html
                projections to
                2060--chrome-extension://oemmndcbldboiebfnladdacbdfmadadm/https:/
                /www.census.gov/content/dam/Census/library/publications/2015/demo
                /p25-1143.pdf

Census Pop Projection 2015 to 2060(
        [(2015,0)-(2060,1.1e+008)],(2015,7.2167e+007),(2020,7.6482e+007),(2025,8.1135e+007
),(2030,8.604e+007),(2035,9.0986e+007),(2040,9.4999e+007),(2045,9.8595e+007
),(2050,1.02091e+008),(2055,1.05491e+008),(2060,1.09252e+008),(2065,0))
Units: People
http://www.census.gov/population/projections/data/national/2014/s
                ummarytables.html table 9. NP2014-T9.xls

Change in AUC=
        TP/divide by this nr of years*"PDF of Threshold for D-"
Units: 1/year

Change in R[group]=
        (Indicated Starting Age for Screening[group]-Recommended Starting Age R[group
])/Time to Adj R[group]*R Switching[group]
Units: Ages/year

Change in Threshold[group]=
        (Desired Threshold[group]-Threshold T[group])/Time to Adj T[group]*Threshold Switching
[group]+PULSE(1990,1)*0.01
Units: 1/year
Yearly rate of change of the Threshold value T

Clinical Detection Switch=
        1
Units: dmnl [0,1,0.5]

Complete Prevalence=
        2.79559e+006
Units: dmnl
In 2012. US Estimated Prevalence counts were estimated by
                applying US populations to SEER 9 Limited Duration Prevalence
                proportions. Counts are prevalence estimates for January 1, 2012
                and based on the SEER November 2014 submission. 2.707.821 in
                2011.

Constant=
        1e-013
Units: dmnl
-3

Cost Biopsy=
        SUM(Biopsy Rate by age[Age!])*Cost of Biopsy
Units: $/year

Cost Continuing Per Year=
        Base Cost Continuing Per Year*Table Eff of T on Cost of Treatment(Technology T
)
Units: $/(year*person)

Cost EOL[Grade]=
        SUM(Cost PCa Deaths[Grade,Treatment!])+Cost Ux PCa Deaths[Grade]+Cost oc Deaths
[Grade]+Cost Ux oc Deaths[Grade]
Units: $/year

Cost Init Treatment[Grade,Treatment]=
        (SUM(txCxM0[Age!,Grade,Treatment])+SUM(txCxM1[Age!,Grade,Treatment])+SUM(txSxM0
[Age!,Grade,Treatment])+SUM(txSxM1[Age!,
        Grade,Treatment]))*One Time Treatment Cost
Units: $/year
Initial cost for PCa is 19.710 $. Annualized Mean Net Costs of
                Care by Age, Gender and Phase of Care (Per Patient). Costs in
                2010 US Dollars.
                http://costprojections.cancer.gov/annual.costs.html.
                http://jnci.oxfordjournals.org/content/103/2/117.long for men
                >65. for men<65 it is on Table 4.

Cost Maintenance[Grade,Treatment]=
        (SUM(Tx CxM0[Age!,Grade,Treatment])+SUM(Tx CxM0M1[Age!,Grade,Treatment])+SUM
(Tx SxM0[Age!,Grade,Treatment])+SUM(Tx SxM0M1
        [Age!,Grade,Treatment]))*Cost Continuing Per Year
Units: $/year
Continuing cost is 3.201 $/year. Annualized Mean Net Costs of
                Care by Age, Gender and Phase of Care (Per Patient). Costs in
                2010 US Dollars.
                http://costprojections.cancer.gov/annual.costs.html.
                http://jnci.oxfordjournals.org/content/103/2/117.long for men
                >65. for men<65 it is on Table 4.

Cost oc Deaths[Grade]=
        Last Year of Life Cost oc Death*(SUM(XXocCxM0[Age!,Grade])+SUM(XXocCxM1[Age
!,Grade])+SUM(XXocSxM0[Age!,Grade])+SUM(XXocSxM1[Age!,Grade]))
Units: $/year

Cost of Biopsy=
        50
Units: $/Biopsies
reference?

Cost of Cancer Care:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'AK19')
Units: 1/year
Cancer survivor: any person diagnosed with cancer, from the time
                of initial diagnosis until his or her death.
                https://costprojections.cancer.gov/graph.php#
                https://costprojections.cancer.gov/annual.costs.html

Cost of Care for PCa=
        19710
Units: dmnl
Initial cost for PCa is 19.710 $, continuing cost is 3.201
                $/year, last year of life cost (if PCa death=62.242$, if other
                cause cost=5370$). Annualized Mean Net Costs of Care by Age,
                Gender and Phase of Care (Per Patient). Costs in 2010 US
                Dollars. http://costprojections.cancer.gov/annual.costs.html.
                http://jnci.oxfordjournals.org/content/103/2/117.long for men
                >65. for men<65 it is on Table 4.

Cost of Care PCa Survivors=
        1
Units: dmnl
Cost of care for cancer patients who die of their disease
                follows a "U-shaped" curve, with the highests costs in the
                initial phase following diagnosis and the phase before death,
                and the lowest costs in the period inbetween, the continuing
                phase. Cost in continuing phase of care is still higher for
                cancer survivors compared with similar individuals without
                cancer. Prostate and female breast cancers had the highest cost
                in the continuing phase. The highest increases in medical cost
                of care in 2020 were projected for female breast (32%) and
                prostate (42%) cance patients in the continuing phase. (Mariotto
                et al., 2010), see Figure 3.

Cost of Care Total PCa=
        11.85
Units: dmnl
http://costprojections.cancer.gov/expenditures.html 11.85
                billion in 2010, 16.34 estimated in 2020. downbload full
                dataset. The lifetime cost to prevent one PCa death is
                $5.277.308. The cost per life-year saved exceeds $262.000
                (Shteynshlyuger, Andriole, 2011-Cost effectiveness of PSA
                screening in the US)

Cost of Prevention=
        Cost PSA+Cost Biopsy
Units: $/year

Cost of PSA Test=
        20

Units: $/tests
15-35 dollars? add reference

Cost of Treatment=
        SUM(Cost of Treatment by grade[Grade!])
Units: $/year

Cost of Treatment by grade[Grade]=
        SUM(Cost Init Treatment[Grade,Treatment!])+SUM(Cost Maintenance[Grade,Treatment
!])+Cost EOL[Grade]
Units: $/year

Cost PCa Deaths[Grade,Treatment]=
        Last Year of Life Cost PCa Death*(SUM(XXpcSxM0[Age!,Grade])+SUM(XXpcSxM1[Age
!,Grade])+SUM(XXpcCxM0[Age!,Grade])+SUM
        (XXpcCxM1[Age!,Grade])+SUM(XXpcTxCxM0[Age!,Grade,Treatment])+SUM(XXpcTxCxM0M1
[Age!,Grade,Treatment])+SUM(XXpcTxSxM0[Age!
        ,Grade,Treatment])+SUM(XXpcTxSxM0M1[Age!,Grade,Treatment]))
Units: $/year
Last year of life cost (if PCa death=62.242$, if other cause
                cost=5370$). Annualized Mean Net Costs of Care by Age, Gender
                and Phase of Care (Per Patient). Costs in 2010 US Dollars.
                http://costprojections.cancer.gov/annual.costs.html.
                http://jnci.oxfordjournals.org/content/103/2/117.long

Cost PSA=
        Cost of PSA Test*SUM(PSA Screening Rate by age[Age!])
Units: $/year

Cost Ux oc Deaths[Grade]=
        Fraction of undiagnosed disease discovered at time of death*(SUM(XXocUxM0[
Age!,Grade])+SUM(XXocUxM1[Age!,Grade]))*Last Year of Life Cost oc Death
Units: $/year
Last year of life cost (if PCa death=62.242$, if other cause
                cost=5370$). Annualized Mean Net Costs of Care by Age, Gender
                and Phase of Care (Per Patient). Costs in 2010 US Dollars.
                http://costprojections.cancer.gov/annual.costs.html.
                http://jnci.oxfordjournals.org/content/103/2/117.long

Cost Ux PCa Deaths[Grade]=
        Fraction of undiagnosed disease discovered at time of death*(SUM(XXpcUxM0[
Age!,Grade])+SUM(XXpcUxM1[Age!,Grade]))*Last Year of Life Cost PCa Death
Units: $/year

Crude Age Specific PCa Incidence Data 1980to2013[AgeGroup35to39]:INTERPOLATE:
:=
        GET XLS DATA('PSA.xlsx','CancerStatisticsDataIncidence','1', 'J10')
Crude Age Specific PCa Incidence Data 1980to2013[AgeGroup40to44]:INTERPOLATE:
        :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataIncidence','1', 'J11')
Crude Age Specific PCa Incidence Data 1980to2013[AgeGroup45to49]:INTERPOLATE:
        :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataIncidence','1', 'J12')
Crude Age Specific PCa Incidence Data 1980to2013[AgeGroup50to54]:INTERPOLATE:
        :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataIncidence','1', 'J13')
Crude Age Specific PCa Incidence Data 1980to2013[AgeGroup55to59]:INTERPOLATE:
        :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataIncidence','1', 'J14')
Crude Age Specific PCa Incidence Data 1980to2013[AgeGroup60to64]:INTERPOLATE:
        :=

GET XLS DATA('PSA.xlsx','CancerStatisticsDataIncidence','1', 'J15')
Crude Age Specific PCa Incidence Data 1980to2013[AgeGroup65to69]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataIncidence','1', 'J16')
Crude Age Specific PCa Incidence Data 1980to2013[AgeGroup70to74]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataIncidence','1', 'J17')
Crude Age Specific PCa Incidence Data 1980to2013[AgeGroup75to79]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataIncidence','1', 'J18')
Crude Age Specific PCa Incidence Data 1980to2013[AgeGroup80plus]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataIncidence','1', 'J23')
    Units: People/year
    Incidence rates are per 100000 and are age-adjusted to the 2000
                    US Std Population (19 age groups - Census P25-1130). SEER
                    November 2015 submission. SEER 9 areas Sheet
                    "CancerStatisticsDataIncidence"
                    http://seer.cancer.gov/canstat/animator

Crude Age Specific PCa Mortality[Age]=
        Annual Mortality PCa by Age[Age]*per100000men
Units: People/year

Crude Age Specific PCa Mortality Data 1980to2013[AgeGroup35to39]:=
        GET XLS DATA('PSA.xlsx','CancerStatisticsDataPCa','1', 'P10')
Crude Age Specific PCa Mortality Data 1980to2013[AgeGroup40to44]:=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataPCa','1', 'P11')
Crude Age Specific PCa Mortality Data 1980to2013[AgeGroup45to49]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataPCa','1', 'P12')
Crude Age Specific PCa Mortality Data 1980to2013[AgeGroup50to54]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataPCa','1', 'P13')
Crude Age Specific PCa Mortality Data 1980to2013[AgeGroup55to59]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataPCa','1', 'P14')
Crude Age Specific PCa Mortality Data 1980to2013[AgeGroup60to64]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataPCa','1', 'P15')
Crude Age Specific PCa Mortality Data 1980to2013[AgeGroup65to69]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataPCa','1', 'P16')
Crude Age Specific PCa Mortality Data 1980to2013[AgeGroup70to74]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataPCa','1', 'P17')
Crude Age Specific PCa Mortality Data 1980to2013[AgeGroup75to79]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataPCa','1', 'P18')
Crude Age Specific PCa Mortality Data 1980to2013[AgeGroup80plus]:INTERPOLATE:
    :=
                GET XLS DATA('PSA.xlsx','CancerStatisticsDataPCa','1', 'P21')
    Units: People/year
    Per 100.000 age -specific crude US mortality rate. 2004-2013.
                    sheet1- B91
                    http://seer.cancer.gov/canstat/animator/#y=2013f;o=0011633;v1=1A0
                    002.4FF0000.20.11

Crude Age Specific PCa Mortality Data 2004to2013[Age]=
        0.0335,0.1864,0.8808,3.2528,8.8254,20.6576,41.8476,80.7456,146.54,799.622
Units: People/year

Per 100.000 age -specific crude US mortality rate. 2004-2013.
    sheet1- B91

Crude Age Specific PCa Mortality Data 2009to2013[Age]=
    0.0364,0.163,0.9016,3.2496,8.7403,19.7391,39.3282,74.8977,133.456,728.594
Units: People/year
Per 100.000 age -specific crude US mortality rate. 2004-2013.
    sheet1- C91 80-84: 233.9645, 85+494.6296

Crude Death Fraction=
    XXTotal/Total Popn
Units: 1/year

Crude Death Rate All Ages=
    XXTotalAllAges/Total Popn All Ages*per100000men
Units: People/year

Crude Death Rate All Ages DATA:=
    GET XLS DATA('PSA.xlsx','Sheet1','2', 'F104')
Units: People/year

Crude Mortality Decrease Projection=
    Total Male Deaths Projected Time Series/1.01e+006
Units: People/year
this is wrong, project by taking into account the popn counts

Crude PCa Death Rate All Ages=
    XXpcTotal/Total Popn All Ages*per100000men
Units: People/year

Crude PCa Deaths Data:INTERPOLATE::=
    GET XLS DATA('PSA.xlsx','Sheet1','2', 'G17')
Units: People/year
all ages, so i have to convert this to crude rate 35+. PCa
        deaths, male, all ages crude death rate, not 35+ But we can
        assume that PCa deaths below 35 is negligible. At CDC compressed
        mortality file it is called "crude rate per 100.000", expressed
        as the number of deaths reported each calendar year per the
        factor you select. The default factor is per 100,000 population,
        reporting the death rate per 100,000 persons. Crude Rate = Count
        / Population * 100,000

Crude PCa Deaths Data 35plus:=
    GET XLS DATA('PSA.xlsx','Sheet2','2', 'F5')
Units: People/year

Crude Rate 35to44=
    XXtotal35to44/Popn 35to44*per100000men
Units: People/year

Crude Rate 45to54=
    XXtotal45to54/Popn 45to54*per100000men
Units: People/year

Crude Rate 55to64=
    XXtotal55to64/Popn 55to64*per100000men
Units: People/year

Crude Rate 65plus=
    XXtotal65plus/Total Popn above 65*per100000men
Units: People/year

Crude Rate 65to74=
        XXtotal65to74/Popn 65to74*per100000men
Units: People/year

Crude Rate 75plus=
        XXtotal75plus/Popn 75plus*per100000men
Units: People/year

Crude Rate All Ages=
        SUM(XXTotalbyAge[Age!])/Total Popn*per100000men
Units: People/year
At CDC compressed mortality file it is called "crude rate per
        100.000", expressed as the number of deaths reported each
        calendar year per the factor you select. The default factor is
        per 100,000 population, reporting the death rate per 100,000
        persons. Crude Rate = Count / Population * 100,000

Crude Rate All Ages Time Series 1979to2014:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F56')
Units: People/year
At CDC compressed mortality file it is called "crude rate per
        100.000", expressed as the number of deaths reported each
        calendar year per the factor you select. The default factor is
        per 100,000 population, reporting the death rate per 100,000
        persons. Crude Rate = Count / Population * 100,000 FOR 35+ MALE
        POPULATION

Crude Rate Future Relative to 1990:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'AP33')
Units: People/year
GET XLS DATA('PSA.xlsx','Sheet1','2', 'AP32')

Crude Rate Future Time Series:=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'AP31')
Units: People/year

Crude RateTime Series 35to44:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F49')
Units: People/year

Crude RateTime Series 45to54:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F50')
Units: People/year

Crude RateTime Series 55to64:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F51')
Units: People/year

Crude RateTime Series 65to74:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F52')
Units: People/year

Crude RateTime Series 75plus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F68')
Units: People/year
At CDC compressed mortality file it is called "crude rate per
        100.000", expressed as the number of deaths reported each
        calendar year per the factor you select. The default factor is
        per 100,000 population, reporting the death rate per 100,000
        persons. Crude Rate = Count / Population * 100,000

Crude RateTime Series 75to84:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F53')
Units: People/year

Crude RateTime Series 85plus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F54')
Units: People/year

Crude Total PCa Mortality=
        ZIDZ(SUM(XXpcbyAge[Age!]),SUM(Total Popn by age[Age!]))*per100000men
Units: People/year

Crude XXpc Model=
        XXpcTotal/Total Popn*per100000men
Units: People/year

Cum Cost by Grade[Grade]=
        Cum Total Cost PSA and Biopsy by Grade[Grade]+Cum Total Cost Treatment by Grade
[Grade]
Units: $
1.38e+007 in 2010. Assuming constant incidence, survival, and
                cost, projection is 13.8 and 18.1 million cancer survivors in
                2010 and 2020, respectively, with associated costs of cancer
                care of 124.57 and 157.77 billion 2010 US dollars.
                http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
                survivor: any person diagnosed with cancer, from the time of
                initial diagnosis until his or her death.
                http://costprojections.cancer.gov/cancer.prevalance.html

Cum Cost Treatment[Grade,Treatment]=
        SUM(Cum Total Cost Maintenance[Grade!,Treatment])+SUM(Cum Total Cost Initial Treatment
[Grade!,Treatment])+SUM(Cum Total Cost End of Life Care[Grade!,Treatment])
Units: $

Cum Nr Biopsies= INTEG (
        SUM(Biopsy Rate by age[Age!]),
                0)
Units: Biopsies
cumulative number of unnecessary biopsies is a practically
                meaningfu variable

Cum Nr of Deaths due Unnecessary Biopsy= INTEG (
        SUM(Deaths Per Year due Unnecessary Biopsy[Age!]),
                0)
Units: People

Cum Nr of FPs= INTEG (
        SUM(FP Rate Per Year[Age!]),
                0)
Units: FP

Cum Nr of Men who Ever Had a FP= INTEG (
        SUM(First Time FP Rate Per Year[Age!]),
                0)
Units: People

Cum Nr of Men who Ever Had an Unnecessary Biopsy= INTEG (
        SUM(People with Unnecessary Biopsies Per Year[Age!]),
                0)
Units: People

Wilt et al., 2014--For 1000 men undergoing screening every 1 to
4 years and followed for up to 14 years, approximately 1 in 4
will have an elevated PSA test (80% are false positive), and
most will undergo at least one set of prostate biopsies, often
more than one. Among men undergoing a biopsy, one-third or more
will incur at least moderate harm such as pain, bleeding, and
infection. Between one and seven in 100 will be hospitalized
within 30 days, typically for sepsis, many with
antibiotic-resistant organisms (1,2).--
http://www.uptodate.com/contents/screening-for-prostate-cancer
1. Moyer VA. Screening for prostate cancer: US Preventive
Services Task Force recommendation statement. Ann Intern Med.
2012;157(2):120-123. 2. Basch E, Oliver TK, Vlckers A, et al.
Screening for prostate cancer with prostate-specific antigen
testing: American Society of Clinical Oncology provisional
clinical opinion.yC//« O?icol. 2012;30(24):3020-3025. RISKS OF
BIOPSY--Although early reports indicated that prostate biopsies
very rarely (<1 percent) caused complications (eg, bleeding,
infection) serious enough to require hospitalization [144], more
recent studies suggest both higher rates of infectious
complications and that the rate of infectious complications may
be increasing over time [145-148]. Hospitalization rates for
infectious complications in these studies have ranged from 0.6
to 4.1 percent [147]. Infectious complications can lead to
sepsis, which can very rarely lead to death. A modeling study,
assuming a biopsy mortality rate of 0.2 percent [149], concluded
that prostate cancer screening could be associated with a net
increased overall mortality, particularly under the conditions
that biopsy rates are high and screening is relatively
ineffective [150]. However, other studies have suggested much
lower mortality rates following biopsy [147]. Population-based
studies include an analysis of US Medicare data that found a
mortality rate of 0.3 percent in the 30 days following biopsy;
this was actually 70 percent lower than the 30-day mortality in
a comparison population not undergoing biopsy [145]. An analysis
of registry data from Canada found a 30-day mortality rate of
0.09 percent [146]. Randomized trials with follow-up on 1147
biopsies [151], and 10,474 biopsies [152], reported no
biopsy-related deaths. Prostate biopsy can also lead to anxiety
and physical discomfort [153]. Among 116 men undergoing biopsy
in the Rotterdam screening study, 55 percent reported discomfort
with the procedure, including 2 percent who had pain persisting
longer than one week. Being diagnosed with prostate cancer is
psychologically distressing, but even patients with a negative
biopsy result may be distressed [154,155]. Chronic anxiety can
follow a negative prostate biopsy because this apparently
favorable result cannot completely rule out prostate cancer
given the relatively high false-negative biopsy rate [156].

Cum Nr of PSA Tests for Dminus= INTEG (
        SUM(Screening Rate wo Disease[Age!]),
                0)
Units: tests
should be zero until screening starts in 1987-88

Cum Nr of PSA Tests for DxDplus= INTEG (
        SUM(Screening Rate of Dx[Age!]),
                0)
Units: tests
should be zero until screening starts in 1987-88

Cum Nr of PSA Tests for TxDplus= INTEG (
        SUM(Screening Rate of Tx[Age!,Treatment!]),
                0)
Units: tests
should be zero until screening starts in 1987-88

Cum Nr of PSA Tests for UxDplus= INTEG (
        SUM(Screening Rate of Ux[Age!,Grade!]),
                0)
Units: tests
should be zero until screening starts in 1987-88

Cum Nr of Unnecessary Biopsies= INTEG (
        SUM(Unnecessary Biopsy Rate by age[Age!]),
                0)
Units: Biopsies
cumulative number of unnecessary biopsies is a practically
                meaningfu variable. estimates are available, in the range of
                millions.

Cum Nr PCa Cases Diagnosed=
        Cum Total Cx PCa+Cum Total Sx PCa
Units: People
total number of (indolent,nonprogressive+progressive) cancers
                detected (clinically or by screening), since the beginning of
                the simulation. Data on 349.154 PCa cases diagnosed since 1986
                have been entered to the Amer. College of Surgeons Nat. Cancer
                DataBase (NCDB). Mettlin et al., 1996. Data can be used to
                describe patterns of presentation, treatment, and outcome
                associated with PCa. http://oliver.facs.org/BMPub/index.cfm

Cum Nr PSA Tests=
        Cum Nr of PSA Tests for Dminus+Cum Nr of PSA Tests for UxDplus+Cum Nr of PSA Tests for TxDplus
+Cum Nr of PSA Tests for DxDplus
Units: tests
Total number of PSA tests, number given in some articles,
                compared against each other by 3 CISNET models, for period:
                1985-2000? The role of PSA testing patterns in the recent PCa
                incidence decline in the US (Legre et al., 1998)

Cum Total Cost End of Life Care[Grade,Treatment]= INTEG (
        Cost oc Deaths[Grade]+Cost PCa Deaths[Grade,Treatment]+Cost Ux oc Deaths[Grade
]+Cost Ux PCa Deaths[Grade],
                0)
Units: $

Cum Total Cost Initial Treatment[Grade,Treatment]= INTEG (
        Cost Init Treatment[Grade,Treatment],
                0)
Units: $

Cum Total Cost Maintenance[Grade,Treatment]= INTEG (
        Cost Maintenance[Grade,Treatment],
                0)
Units: $
1.38e+007 in 2010. Assuming constant incidence, survival, and
                cost, projection is 13.8 and 18.1 million cancer survivors in
                2010 and 2020, respectively, with associated costs of cancer
                care of 124.57 and 157.77 billion 2010 US dollars.
                http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
                survivor: any person diagnosed with cancer, from the time of

initial diagnosis until his or her death.
http://costprojections.cancer.gov/cancer.prevalance.html

Cum Total Cost of Biopsies= INTEG (
        Cost Biopsy,
                0)
Units: $
should be zero before 1987-88

Cum Total Cost of PSA Test= INTEG (
        Cost PSA,
                0)
Units: $
should be zero before 1987-88

Cum Total Cost PSA and Biopsy by Grade[Grade]= INTEG (
        Cost of Prevention,
                0)
Units: $
http://costprojections.cancer.gov/expenditures.html 11.85
                billion in 2010, 16.34 estimated in 2020. downbload full
                dataset. The lifetime cost to prevent one PCa death is
                $5.277.308. The cost per life-year saved exceeds $262.000
                (Shteynshlyuger, Andriole, 2011-Cost effectiveness of PSA
                screening in the US)

Cum Total Cost Treatment=
        SUM(Cum Total Cost Treatment by Grade[Grade!])
Units: $

Cum Total Cost Treatment by Grade[Grade]= INTEG (
        Cost of Treatment by grade[Grade],
                0)
Units: $
http://costprojections.cancer.gov/expenditures.html 11.85
                billion in 2010, 16.34 estimated in 2020. downbload full
                dataset. The lifetime cost to prevent one PCa death is
                $5.277.308. The cost per life-year saved exceeds $262.000
                (Shteynshlyuger, Andriole, 2011-Cost effectiveness of PSA
                screening in the US)

Cum Total Cx Indolent PCa=
        1
Units: People
indolent disease cant get detected clinically, so this stock has
                to be zero

Cum Total Cx PCa= INTEG (
        SUM(cxRatePCa[Age!,Grade!]),
                0)
Units: People
total number of clinically-detected people with PCa, they are
                relevant cases Q: for screen detections we have an estimate. do
                we have an estimate for clinical detections?

Cum Total oc Deaths AtRisk= INTEG (
        SUM(XXocTotalAtRisk by Age[Age!]),
                0)
Units: People

Cum Total oc Deaths Distant= INTEG (

SUM(XXocDistant[Age!,Grade!]),
                0)
Units: People

"Cum Total oc Deaths Loco-regional"= INTEG (
        SUM(XXocLocoReg[Age!,Grade!]),
                0)
Units: People

Cum Total oc Deaths of Men with PCa= INTEG (
        SUM(XXocDplusbyAge[Age!]),
                0)
Units: People

Cum Total Overdiagnosed=
        SUM(Cum Total Overdiagnosed by age[Age!])
Units: People
Welch and Albertsen, 2009. JNCI. PCa diagnosis and treatment
                after the introduction of PSA Screening: 1986-2005. vol 101. no
                19. pp 1325-29. Over a million American men. Overdiagnosis other
                harms: suicide, bankruptcy, loss of inner calm, Welch book 204.

Cum Total Overdiagnosed by age[Age]=
        SUM(Cum Total Overdiagnosed by age grade[Age,Grade!])
Units: People
Welch and Albertsen, 2009. JNCI. PCa diagnosis and treatment
                after the introduction of PSA Screening: 1986-2005. vol 101. no
                19. pp 1325-29. Over a million American men. Overdiagnosis other
                harms: suicide, bankruptcy, loss of inner calm, Welch book 204.

Cum Total Overdiagnosed by age grade[Age,Grade]=
        Cum Total Overdiagnosed Cx PCa+Cum Total Overdiagnosed Sx PCa
Units: People
Welch and Albertsen, 2009. JNCI. PCa diagnosis and treatment
                after the introduction of PSA Screening: 1986-2005. vol 101. no
                19. pp 1325-29. Over a million American men. Overdiagnosis other
                harms: suicide, bankruptcy, loss of inner calm, Welch book 204.

Cum Total Overdiagnosed by grade[Grade]=
        SUM(Cum Total Overdiagnosed by age grade[Age!,Grade])
Units: People
Welch and Albertsen, 2009. JNCI. PCa diagnosis and treatment
                after the introduction of PSA Screening: 1986-2005. vol 101. no
                19. pp 1325-29. Over a million American men. Overdiagnosis other
                harms: suicide, bankruptcy, loss of inner calm, Welch book 204.

Cum Total Overdiagnosed Cx PCa= INTEG (
        SUM(XXocCxPCa by age grade[Age!,Grade!]),
                0)
Units: People
overdiagnosis of distant disease due to death of other causes??
                overdiagnosis occurs by the time of death of other causes.

Cum Total Overdiagnosed Sx PCa= INTEG (
        SUM(XXocSxPCa by age grade[Age!,Grade!]),
                0)
Units: People
overdiagnosis of locoregional disease due to death of other
                causes. sould be zer before PSA starts in 1987-88. overdiagnosis
                occurs by the time of death of other causes.

Cum Total Overdiagnosed SxIndolent= INTEG (
        dxRateSxIndolent,
                0)
Units: People
should be zero until PSA screening starts in 1987-88, this is
                pure overdiagnosis of indolent disease. overdiagnosis by the
                time of detection.

Cum Total Overtreated=
        Cum Total Overtreated Cx PCa+Cum Total Overtreated Sx PCa
Units: People

Cum Total Overtreated Cx PCa= INTEG (
        pp2,
                0)
Units: People

Cum Total Overtreated Indolent=
        1
Units: People
should be zero until PSA screening starts in 1987-88, this is
                pure overtreatment of indolent disease.

Cum Total Overtreated Sx PCa= INTEG (
        pp,
                0)
Units: People

Cum Total PCa Deaths Distant[Grade]= INTEG (
        SUM(XXpcM1 by age grade[Age!,Grade]),
                0)
Units: People
seer data for cumulative

Cum Total PCa Deaths Locoregional[Grade]= INTEG (
        SUM(XXpcM0 by age grade[Age!,Grade]),
                0)
Units: People

Cum Total PCa Deaths of Men with PCa= INTEG (
        SUM(XXpcbyAge[Age!]),
                0)
Units: People

Cum Total PCa Deaths TxDistant[Grade]= INTEG (
        SUM(XXpcTxDistant[Grade,Treatment!]),
                0)
Units: People

Cum Total PCa Deaths TxLocoregional[Grade]= INTEG (
        SUM(XXpcTxLocoReg[Grade,Treatment!]),
                0)
Units: People

Cum Total Sx Indolent PCa=
        1
Units: People
total number of screen-detected people treated with indolent
                disease, they are overtreated

Cum Total Sx PCa= INTEG (

```
            SUM(sxRatePCa[Age!,Grade!]),
                        0)
Units: People
total number of screen detected people with PCa, they are
                    relevant cases

Cum Total TxCx Indolent PCa=
        1
Units: People
total number of clinically-detected people treated with indolent
                    disease, they are overtreated

Cum Total TxCx PCa[Age,Grade]= INTEG (
        SUM(txRateCxPCa[Age,Grade,Treatment!]),
                        0)
Units: People
total number of clinically-detected people treated with PCa,
                    they are relevant cases where screening could advance the
                    diagnosis

Cum Total TxInd PCa=
        1
Units: People

Cum Total TxM0 PCa= INTEG (
        SUM(txRateM0[Age!,Grade!,Treatment!]),
                        0)
Units: People

Cum Total TxM1 PCa= INTEG (
        SUM(txRateM1[Age!,Grade!,Treatment!]),
                        0)
Units: People

Cum Total TxSx Indolent PCa=
        1
Units: People
total number of screen-detected people treated with indolent
                    disease, they are overtreated

Cum Total TxSx PCa[Age,Grade]= INTEG (
        SUM(txRateSxPCa[Age,Grade,Treatment!]),
                        0)
Units: People
total number of screen-detected people treated with PCa, they
                    are relevant cases

CumTotal CxTxPCa=
        SUM(Cum Total TxCx PCa[Age!,Grade!])
Units: People

CumTotal SxTxPCa=
        SUM(Cum Total TxSx PCa[Age!,Grade!])
Units: People
FIRST OVER GRADE THEN OVER TREATMENT

CumTotal TxPCa=
        CumTotal CxTxPCa+CumTotal SxTxPCa
Units: People

Cumulative Net Migration 35plus Male= INTEG (
```

Adult Net Immigration,
　　　　0)
Units: People

Current Cost=
　　　　SUM(Current Cost by grade[Grade!])
Units: $/year

"Current Cost ($/yr)"=
　　　　1
Units: dmnl

Current Cost by grade[Grade]=
　　　　Cost of Prevention+Cost of Treatment by grade[Grade]
Units: $/year

Current Screened Fraction[Age]=
　　　　Screen Eligible Fraction[Age]*Adoption Fraction F
Units: dmnl
Probability of getting a PSA screening test, changes between
　　　　　　0-1, AGE ADJUSTED

Current Screened Fraction 40s=
　　　　SUM(Current Screened Fraction[AgeGroup40to49!]*Total Popn by age[AgeGroup40to49
!])/SUM(Total Popn by age[AgeGroup40to49!])
Units: dmnl
IS IT THE SAME AS: Fract of popn ever screened? Probability of
　　　　　　getting a PSA screening test, changes between 0-1.

Current Screened Fraction 50s=
　　　　SUM(Current Screened Fraction[AgeGroup50to59!]*Total Popn by age[AgeGroup50to59
!])/SUM(Total Popn by age[AgeGroup50to59!])
Units: dmnl
IS IT THE SAME AS: Fract of popn ever screened? Probability of
　　　　　　getting a PSA screening test, changes between 0-1.

Current Screened Fraction 60s=
　　　　SUM(Current Screened Fraction[AgeGroup60to69!]*Total Popn by age[AgeGroup60to69
!])/SUM(Total Popn by age[AgeGroup60to69!])
Units: dmnl
IS IT THE SAME AS: Fract of popn ever screened? Probability of
　　　　　　getting a PSA screening test, changes between 0-1.

Current Screened Fraction 70s=
　　　　SUM(Current Screened Fraction[AgeGroup70to79!]*Total Popn by age[AgeGroup70to79
!])/SUM(Total Popn by age[AgeGroup70to79!])
Units: dmnl
IS IT THE SAME AS: Fract of popn ever screened? Probability of
　　　　　　getting a PSA screening test, changes between 0-1.

Current Screened Fraction Over 50=
　　　　SUM(Current Screened Fraction[Age50Plus!]*Total Popn by age[Age50Plus!])/SUM
(Total Popn by age[Age50Plus!])
Units: dmnl
IS IT THE SAME AS: Fract of popn ever screened? Probability of
　　　　　　getting a PSA screening test, changes between 0-1.

Current Screened Fraction Over 65=
　　　　SUM(Current Screened Fraction[Age65Plus!]*Total Popn by age[Age65Plus!])/SUM
(Total Popn by age[Age65Plus!])
Units: dmnl

Probability of getting a PSA screening test, changes between 0-1.

Current Screened Fraction Under 50=
         SUM(Current Screened Fraction[AgeUnder50!]*Total Popn by age[AgeUnder50!])
/SUM(Total Popn by age[AgeUnder50!])
Units: dmnl
IS IT THE SAME AS: Fract of popn ever screened? Probability of
             getting a PSA screening test, changes between 0-1.

Current Screened Fraction Under 65=
         SUM(Current Screened Fraction[AgeUnder65!]*Total Popn by age[AgeUnder65!])
/SUM(Total Popn by age[AgeUnder65!])
Units: dmnl
IS IT THE SAME AS: Fract of popn ever screened? Probability of
             getting a PSA screening test, changes between 0-1.

Cutoff X=
         Constant+(Time-INITIAL TIME)/divide by this nr of years
Units: dmnl
This used to be: Constant+(Time-INITIAL TIME)/divide by this
             number of years= -10+Time/2 Threshold value T for the Test
             Outcome.

Cx Distant M1[Age,Grade]= INTEG (
         cxM1[Age,Grade]+mxCxM0[Age,Grade]-SUM(txCxM1[Age,Grade,Treatment!])-XXocCxM1
[Age,Grade]-XXpcCxM1[Age,Grade]+EnterAgeCxM1
         [Age,Grade]-LeaveAgeCxM1[Age,Grade]+ImmCxM1[Age,Grade],
             Adult men popn millions initial 1980[Age]*Init Fract Dplus[Age]*(1-Init Fract M0
[Grade])*(1-Init Fract UxM1)*(1-Init Fract DxTxM1
)*1/3*3*Init Grade[Grade])
Units: People
Clinically detected distant-metastasized cancer (M1). M1
             corresponds to Clinical stage D, lymph node involvement or
             distant metastases. Represents distant cancer based on SEER.

Cx LocoRegional M0[Age,Grade]= INTEG (
         cxM0[Age,Grade]-mxCxM0[Age,Grade]-SUM(txCxM0[Age,Grade,Treatment!])-XXocCxM0
[Age,Grade]-XXpcCxM0[Age,Grade]+EnterAgeCxM0
         [Age,Grade]-LeaveAgeCxM0[Age,Grade]+ImmCxM0[Age,Grade],
             Adult men popn millions initial 1980[Age]*Init Fract Dplus[Age]*Init Fract M0
[Grade]*(1-Init Fract UxM0)*(1-Init Fract DxTxM0
)*1/3*3*Init Grade[Grade])
Units: People
Clinically detected locoregional cancer (M0), plus screen
             detected cancers which represent clinically? NO

Cx M0 High=
         0
Units: People
Clinical stage A, Clinically localized and nonpalpable on DRE.
             Represents local (stage I) cancer based on SEER. Clinically
             localized cancers include T1 and T2 tumors. SEER data assigns
             cancer stage using clinical and pathological data. Hoffman 2003,
             refs 11-13. The SEER Program collects data on cancer incidence,
             treatment, and mortality from cancer registries that cover
             approx. 14% of the US population, and believed to be reasonably
             representative o the US. Nat. Canc. Inst. SEER program.
             Available at: http://seer.cancer.gov/ T1 tumors are defined as
             confined to the prostate with a normal DRE and no positive
             scans, or evidence of metastasis. T2 tumors are defined as
             comfined to the prostate with abnormal or suspicious DRE's, but

218

no positive scans or evidence of metastasis. (Hoffman et al., 2003).Localized: An invasive malignant neoplasm confined entirely to the organ of origin.

Cx M1 High=
        0
Units: People
Clinical stage C, regional. Represents local (stage III) cancer
                based on SEER. T1-T2-T3 are preclinical stages, T4 is clinical
                (Hoffman et al., 2003). Clinical stage C and D, palpable with
                clinical evidence of local extension beyond the prostate; D,
                lymph node involvement or distant metastases. Represents
                regional and distant (stages III and IV) cancer based on SEER.
                Staging guidelines used by SEER categorize all organ-confined
                tumors as stage B (Fleming Cooper and Henson et al., AJCC Cancer
                Staging Manual, 1997). REGIONAL AND DISTANT. Advanced cancers
                include T3 tumors as extending beyond the prostate without
                positive scans or evidence of metastasis and T4 tumors defined
                as having at least 1 positive scan, positive lymph node, or
                distant metastasis (Hoffman et al., 2003).

cxM0[Age,Grade]=
        Ux LocoRegional M0[Age,Grade]*Premetastasis Clinical Diagnosis Hazard Cx[Grade
]*Clinical Detection Switch
Units: People/year
Clinical detection rate of local-regional, low-grade (M0G0)
                disease+ Clinical representation rate of loco-regional,
                low-grade cancer (M0G0). clinically detected vs. clinical
                presentation..

CxM0 age grade[Age,Grade]=
        Cx LocoRegional M0[Age,Grade]
Units: People

cxM1[Age,Grade]=
        Ux Distant M1[Age,Grade]*Postmetastasis Clinical Diagnosis Hazard MCx[Grade
]*Clinical Detection Switch
Units: People/year
Clinical detection rate of metastasized, low-grade (M1G0)
                disease+ Clinical representation rate of distant, low-grade
                (M1G0) disease

CxM1 age grade[Age,Grade]=
        Cx Distant M1[Age,Grade]
Units: People

cxRatePCa[Age,Grade]=
        cxM0[Age,Grade]+cxM1[Age,Grade]
Units: People/year
clinically detected cancer rate per year

cxRatePCa by age[Age]=
        SUM(cxRatePCa[Age,Grade!])
Units: People/year

cxRateTotal=
        SUM(cxRatePCa[Age!,Grade!])
Units: People/year
is it that low when compared to screen detection?

Data Estimated Prob of PCa Deaths(

[(1980,0)-(2000,0.1)],(1980,0),(1987.9,0),(1988,0.071),(1989,0.062),(1990,
0.052),(1991,0.044),(1992,0.033),(1993,0.027),(1993.1,0),(2050,0))
Units: dmnl
The role of PSA testing patterns in the recent PCa incidence
                decline in the US (Legre et al., 1998)

Data for Threshold T(
        [(1990,0)-(2040,4)],(1990,4),(2000,4))
Units: 1/year
Effect of lowering PSA cutoffs-- Some investigators have
                suggested using a lower PSA cutoff because some men with PSA
                levels below 4 ng/mL and normal digital rectal examinations are
                found to have prostate cancer
                [52-55].http://www.uptodate.com/contents/screening-for-prostate-c
                ancer

Data Number of PSA tests(
        [(1988,0)-(2000,20000)],(1988,530),(1989,1776),(1990,3433),(1991,8186),(1992
,12000),(1993,12022))
Units: dmnl
The role of PSA testing patterns in the recent PCa incidence
                decline in the US (Legre et al., 1998)

Data PCa from NCDB 2003to2013=
        1
Units: dmnl
Data on 349.154 PCa cases diagnosed since 1986 have been entered
                to the Amer. College of Surgeons Nat. Cancer DataBase (NCDB).
                Mettlin et al., 1996. Data can be used to describe patterns of
                presentation, treatment, and outcome associated with PCa.
                http://oliver.facs.org/BMPub/index.cfm

Data Percent Ever Had PSA Test(
        [(1988,0)-(2000,100)],(1988,0),(1989,0),(1990,0),(1991,0),(1992,0),(1993,0
),(1994,0),(1995,0),(1996,0),(1997,0),(1998,0),(1999,34.1),(2000,56.8))
Units: dmnl
PSA test use reported in the 2000 NHIS (National Health
                Interview Survey) Ross et al., 2004. Ross et al., 2011 compares
                2000 versus 2005 NHIS
                --http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3056036/ men over
                40 years old, self-report.
                http://archinte.jamanetwork.com/article.aspx?articleid=770031

Data Prevalence PSA test NHIS(
        [(1995,0)-(2015,50)],(1988,0),(1989,0),(1990,0),(1991,0),(1992,0),(1993,0)
,(1994,0),(1995,0),(1996,0),(1997,0),(1998,0),(1999,0),(2000,34),(2005,34),
(2010,36),(2013,31))
Units: dmnl
We examined PSA screening data from the 2000, 2005, 2010, and
                2013 National Health Interview Survey (NHIS). Males aged 50
                years or older who reported PSA testing within the 12 months
                preceding each year's surveywere considered to have undergone
                screening. Sammon et al., 2015. JAMA

Data Rate of First PSA Testing(
        [(1985,0)-(2000,15)],(1985,0),(1986,0),(1987,0),(1988,0.6165),(1989,2.7334
),(1990,4.124),(1991,10.384),(1992,12.937),(1993,10.767),(1994,7.87),(1995,
2.792),(1996,2.584),(1997,2.738),(1998,2.603),(1999,2.685),(2000,2.549))
Units: dmnl
First PSA, per 100 men
                years--http://jnci.oxfordjournals.org/content/102/5/352.full.pdf+

html

Data Rate of Second PSA Testing(
        [(1985,0)-(2000,30)],(1985,0),(1986,0),(1987,0),(1988,0.035),(1989,0.771),
(1990,2.381),(1991,5.296),(1992,11.411),(1993,18.106),(1994,23.349),(1995,26.048
),(1996,25.839),(1997,26.358),(1998,26.949),(1999,27.6127),(2000,27.914))
Units: dmnl
Repeat PSA, per 100 men
                years--http://jnci.oxfordjournals.org/content/102/5/352.full.pdf+
                html

Data Source=
        1
Units: dmnl
Source name: Based on IARC and WHO data Source link:
                http://spreadsheets.google.com/pub?key=phAwcNAVuyj2S9phBhTP3dw&gi
                d=1

Death Rate Biopsy=
        2/1000
Units: dmnl
1.3 per 1000 for healthy, 3.5 per 1000 for men with cancer
                http://www.hopkinsmedicine.org/news/media/releases/johns_hopkins_
                study_reveals_significant_rise_in_prostate_biopsy_complications_a
                nd_high_post_procedure_hospitalization_rate
                http://meetinglibrary.asco.org/content/113206-132 Numbers are
                small enough not to be included in the pop sector as an outflow?
                At 120 days, 1.3 per 1000 biopsies done in men w/o cancer, rates
                are 3.5 per 1000 men for men with a positive cancer.
                http://www.medscape.com/viewarticle/805575. Among men undergoing
                a biopsy, one-third or more will incur at least moderate harm
                such as pain, bleeding, and infection. Between one and seven in
                100 will be hospitalized within 30 days, typically for sepsis,
                many with antibiotic-resistant organisms (1,2).--Wilt et al.,
                2014.

Death Rate Prostatectomy=
        0.2
Units: dmnl
estimates range between 0.2-0.5 percent
                http://www.medscape.com/viewarticle/805575

Death rate ratio to 1990 baseline[Age]=
        Death Rate Ratio to 1990 Baseline SeriesAgeGroups1980to2014[Age](Time)
Units: dmnl
IF THEN ELSE(Time<2014, Death Rate Ratio to 1990 Baseline
                SeriesAgeGroups1980to2014[Age](Time), 0.7)

Death rate ratio to 1990 baseline series[AgeUnder65](
        [(1980,0)-(2040,1.2)],(1980,1.1),(1990,1),(2000,0.84),(2010,0.76),(2020,0.71
),(2030,0.71),(2040,0.71))
Death rate ratio to 1990 baseline series[Age65Plus](
                [(1980,0)-(2040,1.2)],(1980,1.1),(1990,1),(2000,0.9),(2010,0.85),(2020,0.82
        ),(2030,0.82),(2040,0.82))
        Units: dmnl
        Values are based on PRISM for 1990-2040, year 1980 is based on
                        Vital Statistics (Historical Abstracts of the US 2012) comparing
                        1980 to 1990. We are assuming a mortality decrease 1980-1990 in
                        line with Vital Statistics, which shows: M 35-44: no decline
                        (299.2 to 310.4); factor 1.037 M 45-54: decline from 767.3 to
                        610.3; factor 0.795 M 55-64: decline from 1815.1 to 1553.4;

factor 0.856 M 65-74: decline from 4105.2 to 3491.5; factor
0.850 M 75-84: decline from 8816.7 to 7888.6; factor 0.895 M
85+: decline from 18801.1 to 18056.6; factor 0.960. For the
under-65 males, let's take the mean of the first 3 above:
0.896, round to 0.90. For the over-65 males, let's take the
mean of the latter 3 above: .902, round to 0.90. age btw 30-65:
[(1980,0)-(2040,1.2)],(1980,1),(1990,1),(2000,0.84),(2010,0.76),(
2020,0.71),(2030,0.71),(2040,0.71) age above 65:
[(1980,0)-(2040,1.2)],(1980,1.1),(1990,1),(2000,0.9),(2010,0.85),
(2020,0.82),(2030,0.82),(2040,0.82)

Death Rate Ratio to 1990 Baseline Series 1980to2014[AgeGroup35to44]:=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F58')
Death Rate Ratio to 1990 Baseline Series 1980to2014[AgeGroup45to54]:=
                GET XLS DATA('PSA.xlsx','Sheet1','2', 'F59')
Death Rate Ratio to 1990 Baseline Series 1980to2014[AgeGroup55to64]:=
                GET XLS DATA('PSA.xlsx','Sheet1','2', 'F60')
Death Rate Ratio to 1990 Baseline Series 1980to2014[AgeGroup65to74]:=
                GET XLS DATA('PSA.xlsx','Sheet1','2', 'F61')
Death Rate Ratio to 1990 Baseline Series 1980to2014[AgeGroup75plus]:=
                GET XLS DATA('PSA.xlsx','Sheet1','2', 'F69')
        Units: dmnl
Death rate ratio to 1990 baseline series2[Age](
        [(1980,0.5)-(2079,1.2)],(1980,0.84),(2000.9,0.84),(2001,0.91),(2028.9,0.91
),(2029,0.86),(2079,0.86))
Units: dmnl
https://www.ssa.gov/oact/NOTES/as120/LifeTables_Tbl_5.html#wp1012
                577: Life Tables for the United States Social Security Area
                1900-2100 Note: The average annual percentage reduction is the
                complement of the exponential of the slope of the least squares
                line through the logarithms of the central death rates.

Death Rate Ratio to 1990 Baseline SeriesAgeGroups1980to2014[AgeGroup35to44]
(
        [(1980,0)-(2040,1.2)],(1980,0.96387),(1981,0.942744),(1982,0.881111),(1983
,0.859789),(1984,0.871743),(1985,0.898442),(1986,0.929541),(1987,0.941898),
(1988,0.972795),(1989,0.990597),(1990,1),(1991,1.00189),(1992,1.02471),(1993
,1.05478),(1994,1.06793),(1995,1.06615),(1996,0.958308),(1997,0.852757),(1998
,0.827904),(1999,0.821118),(2000,0.822197),(2001,0.836071),(2002,0.835579),
(2003,0.82817),(2004,0.793703),(2005,0.793381),(2006,0.780819),(2007,0.757948
),(2008,0.731534),(2009,0.72638),(2010,0.684505),(2011,0.68837),(2012,0.685471
),(2013,0.688692),(2014,0.698034),(2040,0.6))
Death Rate Ratio to 1990 Baseline SeriesAgeGroups1980to2014[AgeGroup45to54]
        (
                [(1980,0)-(2040,1.2)],(1980,1.25725),(1981,1.22774),(1982,1.17601),(1983,
        1.1388),(1984,1.1124),(1985,1.10051),(1986,1.07499),(1987,1.06092),(1988,1.03683
        ),(1989,1.01983),(1990,1),(1991,0.987792),(1992,0.964133),(1993,0.968223),
        (1994,0.971118),(1995,0.96654),(1996,0.926804),(1997,0.886158),(1998,0.870122
        ),(1999,0.873502),(2000,0.889395),(2001,0.888412),(2002,0.898899),(2003,0.904798
        ),(2004,0.89087),(2005,0.898244),(2006,0.887102),(2007,0.868095),(2008,0.862196
        ),(2009,0.852529),(2010,0.828934),(2011,0.831228),(2012,0.820577),(2013,0.820413
        ),(2014,0.813531),(2040,0.583))
Death Rate Ratio to 1990 Baseline SeriesAgeGroups1980to2014[AgeGroup55to64]
        (
                [(1980,0)-(2040,2)],(1980,1.16842),(1981,1.14229),(1982,1.11991),(1983,1.11806
        ),(1984,1.10751),(1985,1.10168),(1986,1.075),(1987,1.06138),(1988,1.05252)
        ,(1989,1.02716),(1990,1),(1991,0.979093),(1992,0.949582),(1993,0.946475),(
        1994,0.921687),(1995,0.90166),(1996,0.881885),(1997,0.846218),(1998,0.81851
        ),(1999,0.805953),(2000,0.792242),(2001,0.773638),(2002,0.758317),(2003,0.746666
        ),(2004,0.720466),(2005,0.720852),(2006,0.706497),(2007,0.699416),(2008,0.70154
        ),(2009,0.694201),(2010,0.692335),(2011,0.689502),(2012,0.69536),(2013,0.700639

),(2014,0.706947),(2040,0.533))
Death Rate Ratio to 1990 Baseline SeriesAgeGroups1980to2014[AgeGroup65to74]
    (
        [(1980,0.5)-(2040,1.2)],(1980,1.17578),(1981,1.14556),(1982,1.1262),(1983
,1.12405),(1984,1.10744),(1985,1.10452),(1986,1.08453),(1987,1.06466),(1988
,1.05464),(1989,1.01918),(1990,1),(1991,0.9826),(1992,0.964093),(1993,0.969064
),(1994,0.949687),(1995,0.934782),(1996,0.917968),(1997,0.904267),(1998,0.891343
),(1999,0.880336),(2000,0.853385),(2001,0.829527),(2002,0.810882),(2003,0.784131
),(2004,0.74601),(2005,0.734926),(2006,0.705856),(2007,0.686981),(2008,0.679449
),(2009,0.65602),(2010,0.65161),(2011,0.640468),(2012,0.626205),(2013,0.626091
),(2014,0.623083),(2040,0.5714))
Death Rate Ratio to 1990 Baseline SeriesAgeGroups1980to2014[AgeGroup75plus]
    (
        [(1980,0.5)-(2040,1.2)],(1980,1.15349),(1981,1.12864),(1982,1.10021),(1983
,1.10226),(1984,1.08757),(1985,1.08946),(1986,1.06977),(1987,1.05439),(1988
,1.04981),(1989,1.01653),(1990,1),(1991,0.978937),(1992,0.958401),(1993,0.96988
),(1994,0.949871),(1995,0.939656),(1996,0.917329),(1997,0.893686),(1998,0.880048
),(1999,0.877995),(2000,0.867148),(2001,0.852614),(2002,0.851561),(2003,0.841241
),(2004,0.814175),(2005,0.818019),(2006,0.800221),(2007,0.791059),(2008,0.798168
),(2009,0.784951),(2010,0.789163),(2011,0.793744),(2012,0.797694),(2013,0.810226
),(2014,0.814017),(2040,0.63))
Units: dmnl
Life tables for the US Social Security Area 1900-2100:
        https://www.ssa.gov/oact/NOTES/as120/LifeTables_Tbl_6.html
        adjusted by using life tables old:
        [(1980,0.5)-(2040,1.2)],(1980,1.15349),(1981,1.12864),(1982,1.100
        21),(1983,1.10226),(1984,1.08757),(1985,1.08946),(1986,1.06977),(
        1987,1.05439),(1988,1.04981),(1989,1.01653),(1990,1),(1991,0.9789
        37),(1992,0.958401),(1993,0.96988),(1994,0.949871),(1995,0.939656
        ),(1996,0.917329),(1997,0.893686),(1998,0.880048),(1999,0.877995)
        ,(2000,0.867148),(2001,0.852614),(2002,0.851561),(2003,0.841241),
        (2004,0.814175),(2005,0.818019),(2006,0.800221),(2007,0.791059),(
        2008,0.798168),(2009,0.784951),(2010,0.789163),(2011,0.793744),(2
        012,0.797694),(2013,0.810226),(2014,0.814017),(2040,0.75)
        [(1980,0.5)-(2040,1.2)],(1980,1.08949),(1990,1),(2020,0.753906),(
        2040,0.634233)

Death Rate Ratio to 1990 Baseline SeriesCrude1980to2014(
    [(0,0)-(10,10)],(1980,1.15349),(1981,1.12864),(1982,1.10021),(1983,1.10226
),(1984,1.08757),(1985,1.08946),(1986,1.06977),(1987,1.05439),(1988,1.04981
),(1989,1.01653),(1990,1),(1991,0.978937),(1992,0.958401),(1993,0.96988),(1994
,0.949871),(1995,0.939656),(1996,0.917329),(1997,0.893686),(1998,0.880048),
(1999,0.877995),(2000,0.867148),(2001,0.852614),(2002,0.851561),(2003,0.841241
),(2004,0.814175),(2005,0.818019),(2006,0.800221),(2007,0.791059),(2008,0.798168
),(2009,0.784951),(2010,0.789163),(2011,0.793744),(2012,0.797694),(2013,0.810226
),(2014,0.814017))
Units: dmnl

Deaths=
    0
Units: People/year

Deaths Per Year due Unnecessary Biopsy[Age]=
    Death Rate Biopsy*People with Unnecessary Biopsies Per Year[Age]
Units: People/year

Deaths Time Series 35to44:INTERPOLATE::=
    GET XLS DATA('PSA.xlsx','Sheet1','2', 'F33')
Units: People/year

Deaths Time Series 45to54:INTERPOLATE::=

GET XLS DATA('PSA.xlsx','Sheet1','2', 'F34')
Units: People/year

Deaths Time Series 55to64:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F35')
Units: People/year

Deaths Time Series 65to74:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F36')
Units: People/year

Deaths Time Series 75plus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F66')
Units: People/year

Deaths Time Series 75to84:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F37')
Units: People/year

Deaths Time Series 85plus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F38')
Units: People/year

delta:
        d1,d2

denominator=
        F1+F5+F6
Units: dmnl

Desired Threshold[group]=
        Effective Threshold*Perceived HBR T[group]*Eff Ext Pressure on T
Units: dmnl
Desired Threshold value implied by the HBR and other external
                pressures (other advocacy and interest groups)

dfAll[Age]=
        ocDeathsSwitch*Death rate ratio to 1990 baseline[Age]*Popn death rate US 1990
[Age]*Local vs US multiplier on popn death rate*Adjust dt rate[Age]
Units: 1/year
Popn death rate baseline. All other cause mortality rate,
                fractional death rate, or Hazard of non-PCa death. From US-
                Census, by age group. IF THEN ELSE(Mortality Decrease
                Switch=0,Popn death rate US 1990[Age], Popn death rate US
                1990[Age]*Death rate ratio to 1990 baseline [Age])

dfAverageOC=
        ZIDZ(SUM(dfAll[Age!]*Total Popn by age[Age!]),SUM(Total Popn by age[Age!])
)
Units: 1/year
average death fraction for the whole adult male population
                ZIDZ(SUM(AgeGpMean[Age!]*XXpcM1 by age[Age!]),SUM(XXpcM1 by
                age[Age!]))

dfM0[Grade]=
        0.025,0.0025,0
Units: 1/year
0.02,0.001,0---0.015,0.001,0 1/Survival time M0 cases[Grade].
                0.02,0.001,0 Death fraction for Loco-regional- M0 cancer, it is
                grade-specific. Baseline PCa Survival in absence of Treatment.
                PCa deaths from M0 stage can be small enough to be ignored (as

224

Forrester's Urban Dynamics demolition rate for new and mature businesses). Some models take this as zero and have PCa death outflow only from the M1-metastatic stage. No PCa deaths from the indolent stage. Survival time estimates on SEER survival curves by stage (localized and regional almost 100% at 5 years): 400 for localized, 37.8 for regional cases. In the absence of curative treatment, a cancer diagnosed at the localized stage before the age of 65 years is associated with a specific survival of less than 30%. The median survival of metastatic prostatic cancer is 2 to 3 years.
http://www.ncbi.nlm.nih.gov/pubmed/9410329

dfM1[Grade]=
        0.35,0.25,0
Units: 1/year
(0.25,0.2,0) Mortality rate for patients with metastasized PCa.
                Underwood et al. 2012:
                http://www.ncbi.nlm.nih.gov/pubmed/22302420: varied using 0.07
                from Messing et al. to 0.37 to Aus et al. 5.4 in Sensitivity
                Analysis. age specific, check SEER. Mean duration of D2 is 3.3
                years: Etzioni et al., 1999- Table 2.
                http://www.ncbi.nlm.nih.gov/pubmed/10458357 1/Survival time M1
                cases[Grade]. Death fraction from distant, metastasized-M1 (and
                untreated) disease, grade-specific. Baseline PCa Survival in
                absence of Treatment. 0.2? define as dfALL*dfM1? ANY DIFFERENCE
                BETWEEN SX AND CX TREATED DEATH RATES? DIFFERENCE COMES FROM
                GRADE, TREATMENT TYPE, BUT NOT DETECTION METHOD. The median
                survival of metastatic prostatic cancer is 2 to 3 years.
                http://www.ncbi.nlm.nih.gov/pubmed/9410329

dfM1TxM0[Grade,Treatment]=
        reldfTxforM0M1[Treatment]*dfM1[Grade]
Units: 1/year

dFP=
        ("False Pos Rate (FPR)"[d2]-"False Pos Rate (FPR)"[d1])/tdelta
Units: dmnl

dfTxM0[Grade,Treatment]=
        reldfTxforM0[Treatment]*dfM0[Grade]
Units: 1/year
survival applies only to real progressive cases as latents do
                not benefit from screening.

dfTxM1[Grade,Treatment]=
        dfM1[Grade]*reldfTxforM1[Treatment]
Units: 1/year

Diagnosed frac of advanced cases initial=
        0.9
Units: dmnl

Diagnosed frac of early cases initial=
        0.05
Units: dmnl

Diagnosis=
        0
Units: People/year

diseasestate:

225

Dplus,Dzero,Dminus

Distance To Perfect Test=
            (FP^2+(1-TP)^2)^0.5
Units: dmnl

Disutility Due to Cancer Death=
            Disutility End of Life
Units: dmnl

Disutility Due to Treatment=
            Annual Utility Decrement of Living With Treatment before Metastasis
Units: dmnl

Disutility End of Life=
            0.7
Units: dmnl
Martin et al., 2013. We further assumed that QOL during the 12
                months before death from prostate cancer was associated with an
                additional 0.50 reduction in health state utility. ref 17
                https://www.mja.com.au/journal/2013/198/10/risk-assessment-guide-
                prostate-cancer-screening-decisions-cost-effectiveness

divide by this nr of years=
            1
Units: year

Doctors Weighing on T=
            0.4
Units: dmnl
Public doesnt have much influence on T, its more of a doctors
                decision.. If different thresholds are announced, which one
                doctors are following, on the average. Base initial assumption
                is 40% professionals, 60% other medical and advocacy groups.

DRE fract=
            0.5
Units: dmnl
Test performance-- Urologists have been found to have relatively
                low interrater agreement for detecting prostate abnormalities
                [101]. No data are available for the test performance
                characteristics of DRE in primary care---Clinically localized
                PCa, 50% of them have abnormal DRE Approximately 2 to 3 percent
                of men 50 or more years old who undergo a single DRE have
                induration, marked asymmetry, or nodularity of the prostate. In
                one analysis, an abnormal screening DRE doubled the odds of
                detecting a clinically important cancer (defined as a having a
                tumor volume greater than 0.5 mL) that was confined to the
                prostate [50]. Although screening DRE increased the odds
                likelihood of finding early disease, it was also associated with
                a three- to nine-fold increase in the odds of finding
                extraprostatic extension of tumor (presumably not amenable to
                curative therapy). Sensitivity and specificity — A
                meta-analysis of DRE estimated a sensitivity for detecting
                prostate cancer of 59 percent and a specificity of 94 percent
                [102]. Positive predictive value — The positive predictive
                value of an abnormal DRE for prostate cancer varies from 5 to 30
                percent [48,100,103-106]. A meta-analysis calculated an overall
                positive predictive value of 28 percent [102]. COMBINING PSA AND
                DRE — We suggest not performing digital rectal examination
                (DRE) for prostate cancer screening whether alone or in

226

combination with PSA screening. PSA and DRE are somewhat
complementary, and their combined use can increase the overall
rate of cancer detection [41,48,107-109]. As an example, a
multicenter screening study of 6630 men reported a detection
rate of 3.2 percent for DRE, 4.6 percent for PSA, and 5.8
percent for the two methods combined [48,104]. PSA detected
significantly more of the cancers than digital examination (82
versus 55 percent). Overall, 45 percent of the cancers were
detected only by PSA, while just 18 percent were detected solely
by digital examination. Investigators reported a positive
predictive value of 10 percent for a suspicious digital
examination when the PSA level was normal. However, the positive
predictive value was 24 percent for an elevated PSA level with a
normal digital examination. Among men with a normal PSA level,
abnormalities on DRE appear less likely to be from a cancer if
the PSA concentration is below 1.0 ng/mL than if the PSA
concentration is between 3.0 to 4.0 ng/mL [106].
http://www.uptodate.com/contents/screening-for-prostate-cancer
Although these data suggest a potential benefit for combining
PSA and DRE in detecting prostate cancer, randomized trials have
not confirmed a benefit on prostate cancer outcomes. The ERSPC,
which found a small survival benefit with PSA screening, did not
consistently require DRE [13]. The PLCO found no survival
benefit with combined PSA and DRE screening [15].

DRE Sensitivity=
        0.3
Units: dmnl
Likelihood of referral to biopsy if PSA is below 4 ng/ml. The
        frequency of referral to biopsy among men with PSA below 4 ng/ml
        id based on a study by Schroder et al (1998) which found that
        the sensitivity of DRE is approximately 20% for PSA below 3
        ng/ml and 40% for PSA from 3.0 t0 3.9 ng/ml. (Schroder et al.,
        1998).Men with a negative PSA who are referred to biopsy are
        assumed to comply with a frequency that is similar to that among
        men with a moderately elevated PSA (PSA between 4 and 7 ng/ml).

dTdRandD=
        Technology T*(1-Technology T)*Ref Yield to RD
Units: 1/$

dTP=
        ("True Pos Rate (TPR)"[d2]-"True Pos Rate (TPR)"[d1])/tdelta
Units: dmnl

duration=
        FINAL TIME-INITIAL TIME
Units: year

dxRateM0=
        SUM(dxRateM0 by grade[Grade!])
Units: People/year

dxRateM0 by grade[Grade]=
        SUM(cxM0[Age!,Grade])+SUM(sxM0[Age!,Grade])
Units: People/year

dxRateM1=
        SUM(dxRateM1 by grade[Grade!])
Units: People/year

dxRateM1 by grade[Grade]=
        SUM(cxM1[Age!,Grade])+SUM(sxM1[Age!,Grade])
Units: People/year

dxRatePCa by age[Age]=
        cxRatePCa by age[Age]+sxRatePCa by age[Age]
Units: People/year

dxRateSxIndolent=
        SUM(sxM0[Age!,Latent])
Units: People/year

dxRateTotal=
        sxRateTotal+cxRateTotal
Units: People/year

Economic Burden of PCa=
        1
Units: dmnl
http://bmchealthservres.biomedcentral.com/articles/10.1186/1472-6
                963-11-349#CR10
                http://www.cancernetwork.com/review-article/economics-prostate-ca
                ncer-screening-0

Eff Ext Pressure on C2=
        1+StrengthEffExtPonT*(External pressures-1)
Units: dmnl
external pressures*sensitivity to external
                pressure+(1-sensitivity to external pressure)

Eff Ext Pressure on T=
        Relative Influence of Advocacy Groups^StrengthEffExtPonT
Units: dmnl
Effect of external pressures on Cutoff value C

Eff of T on Harms=
        Table Eff of T on Harms(Technology T)
Units: dmnl

Effect of HBR on Indicated Age for Screening[group]=
        1+HBR Multiplier[group]*(Perceived HBR T[group]-1)
Units: dmnl

Effect of HRT on Harms=
        ZIDZ(Eff of T on Harms,(Table Eff of T on Harms(Init Technology)))
Units: dmnl

Effect of Starting Age on Eligible Fraction[Age]=
        Table Starting Age(AgeGpMean[Age]-Actual Starting Age for Routine Screening
)
Units: dmnl

Effect of Stopping Age on Eligible Fraction[Age]=
        Table Stopping Age(AgeGpMean[Age]-StoppingAge)
Units: dmnl
old formulation: MAX(0, MIN(1, (StoppingAge-AgeGpStart[Age])/
                (2*(AgeGpMean[Age]-AgeGpStart[Age]))))

Effective Recommended Starting Age=
        Public Weighing on R*Recommended Starting Age R[prof]+(1-Public Weighing on R
)*Recommended Starting Age R[advoc]

Units: Ages
Public Weighing on R*Recommended Starting Age R[prof]+(1-Public
Weighing on R)*Recommended Starting Age R[advoc] SUM(Public
Weighing on R[group!]*Recommended Starting Age R[group!])
SUM(Public Weighing on R[group!]*Recommended Starting Age
R[group!])

Effective Threshold=
Threshold T[prof]*Doctors Weighing on T+Threshold T[advoc]*(1-Doctors Weighing on T
)
Units: dmnl
In signal detection theory, overall performance depends both on
accuracy (otherwise known as 'sensitivity') of judgment and
on the threshold (otherwise known as 'bias'). SUM(Doctors
Weighing on T[group!]*Threshold T[group!]) Doctors Weighing on
T*Threshold T[prof]+(1-Doctors Weighing on T)*Threshold T[advoc]

EffectiveTestSensM0[Age]=
Sensitivity*BiopCompM0*BiopDetectM0
Units: dmnl
The model estimates an effective test sensitivity which combines
the probability of a positive PSA test, receipt of biopsy, and
sensitivity of the biopsy to detect latent cancer.
https://resources.cisnet.cancer.gov/registry/site-summary/prostat
e/ (similar to CISNET's MISCAN-PRO AND SCANS models)

EffectiveTestSensM1=
SensM1*BiopCompM1*BiopDetectM1
Units: dmnl

"Empirical AUC, Thompson et al., 2005"=
0.678
Units: dmnl
AUC is interpreted as the average value of sensitivity for all
possible values of specificity, is a measure of the overall
performance of a diagnostic test. AUC can take on any value
between 0 and 1, where a bigger value suggests the better
overall performance of a diagnostic test. Any Prostate Cancer vs
No Prostate Cancer.. http://www.ncbi.nlm.nih.gov/pubmed/15998892
(AUC = 0.678).-- The average area under the receiver operating
characteristic curve across test data sets was 0.74 for total
PSA and 0.76 for the combination tests.
http://www.ncbi.nlm.nih.gov/pubmed/15466981

Empirical AUC2=
0.74
Units: dmnl
Vickers et al., 2010. BMJ. Any Prostate Cancer vs No Prostate
Cancer.. http://www.ncbi.nlm.nih.gov/pubmed/15998892 (AUC =
0.678).-- The average area under the receiver operating
characteristic curve across test data sets was 0.74 for total
PSA and 0.76 for the combination tests.
http://www.ncbi.nlm.nih.gov/pubmed/15466981

Empirical Mean and Median=
1
Units: dmnl
Median is 1. from Wilt et al.,
2014.http://onlinelibrary.wiley.com/doi/10.1002/pros.20417/abstra
ct Mean=1.84 in etzioni et al., 2004?

229

Empirical NPV=
            0.85
Units: dmnl
Negative predictive value--The Prostate Cancer Prevention Trial,
                which biopsied men with normal PSA levels, estimated a negative
                predictive value of 85 percent for a PSA value ≤4.0 ng/mL
                [51].
                http://www.uptodate.com/contents/screening-for-prostate-cancer

Empirical PPV=
            0.3
Units: dmnl
Positive predictive value-- The test performance statistic that
                has been best characterized by screening studies is the positive
                predictive value: the proportion of men with an elevated PSA who
                have prostate cancer.-- Overall, the positive predictive value
                for a PSA level >4.0 ng/mL is approximately 30 percent, meaning
                that slightly less than one in three men with an elevated PSA
                will have prostate cancer detected on biopsy [42,48,49]. For PSA
                levels between 4.0 to 10.0 ng/mL, the positive predictive value
                is about 25 percent [48]; this increases to 42 to 64 percent for
                PSA levels >10 ng/mL [48,50]. However, nearly 75 percent of
                cancers detected within the "gray zone" of PSA values between
                4.0 to 10.0 ng/mL are organ confined and potentially curable
                [48]. The proportion of organ-confined cancers drops to less
                than 50 percent for PSA values above 10.0 ng/mL [48]. Thus,
                detecting the curable cancers in men with PSA levels less than
                10.0 ng/mL presents a diagnostic challenge because the high
                false-positive rate leads to many unnecessary biopsies.
                http://www.uptodate.com/contents/screening-for-prostate-cancer
                The cancer detection rate for PSA in the ERSPC, which used a
                4-year screening interval, decreased from 5.1 percent in the
                first round of screening to 4.4 percent in the second round
                [63]. The positive predictive value for a PSA level of 3.0 ng/mL
                or greater decreased from 29.2 to 19.9 percent.

Empirical Sens=
            1
Units: dmnl
Wilt et al., 2014. A major drawback of PSA for screening and
                early detection is its low specificity. In 65% to 75% of men
                with an elevated PSA level (>3 ng/mL), no cancer is found on
                biopsy (34), and in 80%, no high-grade (Gleason score >7)
                potentially lethal cancer is found (35).-- Sensitivity and
                specificity — The traditional cutoff for an abnormal PSA level
                in the major screening studies has been 4.0 ng/mL [42-45]. The
                American Cancer Society systematically reviewed the literature
                assessing PSA performance [46]. In a pooled analysis, the
                estimated sensitivity of a PSA cutoff of 4.0 ng/mL was 21
                percent for detecting any prostate cancer and 51 percent for
                detecting high-grade cancers (Gleason ≥8). Using a cutoff of
                3.0 ng/mL increased these sensitivities to 32 and 68 percent,
                respectively. The estimated specificity was 91 percent for a PSA
                cutoff of 4.0 ng/mL and 85 percent for a 3.0 ng/mL cutoff. PSA
                has poorer discriminating ability in men with symptomatic benign
                prostatic hyperplasia
                [47].http://www.uptodate.com/contents/screening-for-prostate-canc
                er

Empirical TPR=
            "Table ROC for PSA, Thompson et al., 2005 AUC=0.678"("False Pos Rate (FPR)"

230

[d1])
Units: dmnl

Empirical Values for Overdiagnosis=
          30
Units: dmnl
A study that applied computer-simulation models of PSA testing
                    to SEER cancer incidence data estimated that 29 percent of
                    cancers detected in whites and 44 percent of cancers detected in
                    blacks were overdiagnosed [161]. An updated analysis, that also
                    used ERSPC Rotterdam clinical data, estimated an overdiagnosis
                    fraction ranging from 23 to 42 percent among cancers diagnosed
                    by PSA screening
                    [162].http://www.uptodate.com/contents/screening-for-prostate-can
                    cer The authors found that among men aged 60-84 years, 18%-39%
                    of Caucasian men and 20%-44% of African-American men may be
                    overdiagnosed with PSA screening (9).in Yao and Yao, 2002.

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          Units: People/year
          Rate of entering to the indicated age category, for 10 age
                    groups.

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233

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Estimated PCa Death Fraction=
       ZIDZ(XXpcEstimatedTotal,(XXpcEstimatedTotal+XXocTotal))
Units: dmnl
out of 100%, should be close to 3%

Estimated PCa Death Fraction Data=
       Data Estimated Prob of PCa Deaths(Time)
Units: dmnl

Estimated PCa Death Rate=
       1
Units: dmnl

estimatedPrevelance=
       fractrealprev
Units: dmnl
IT WAS 0.4

Exploration of Technology=
    1
Units: dmnl
Goldman analyzes long term effects of prevention interventions
                for many kinds of diseases, he includes the effects of
                technological developments in health care in his studies (D.
                Goldman et al., 2004) (D. P. Goldman et al., 2015). He studies
                the population of age 65 years and older with a Marcov Model.
                Goldman (2015) also projects the health expenditures by
                analyzing the prevention interventions for reducing the risk
                factors such as diabetes, hypertension, obesity and smoking (D.
                P. Goldman et al., 2009) for the population of age 51 years and
                older. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2759785/
                Goldman et al. 2015, 2004, 2009. Research suggests that
                anticipated treatments for cardiovascular disease, neurologic
                disorders, and cancer could make us live longer but could carry
                a substantial price tag:
                http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2759785/
                http://www.ncbi.nlm.nih.gov/pubmed/16186152

"expMeanD+"=
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Units: dmnl

"expMeanD-"=
        EXP("Mu D-")
Units: dmnl

External pressures=
        1
Units: dmnl
External pressures (dimensionless)

F1=
        dFP*(1-estimatedPrevelance)
Units: dmnl
DminusTplus, false positives

F11=
        F1*weight
Units: dmnl
what they think is the fraction of false positives

F11component=
        F11*UtilityDminusTplus2
Units: dmnl

F1component=
        F1*UtilityDminusTplus2
Units: dmnl

F2=
        dTP*estimatedPrevelance*(fracindolent)
Units: dmnl
DzeroTminus, indolent disease detected by screening

F22=
        (F2+F3)*weight+PDplus*(1-weight)
Units: dmnl
what they think is the fraction of D+

F22component=
    F22*UtilityDplusTplus2
Units: dmnl

F2component=
    F2*UtilityDzeroTplus2
Units: dmnl

F3=
    dTP*estimatedPrevelance*(1-fracindolent)
Units: dmnl
DplusTplus, relative cases detected by screening

F33=
    F4*weight+PDminus*(1-weight)
Units: dmnl

F33component=
    F33*UtilityDminusTminus2
Units: dmnl

F3component=
    F3*UtilityDplusTplus2
Units: dmnl

F4=
    -dFP*(1-estimatedPrevelance)
Units: dmnl
DminusTminus, true negatives

F44=
    (F5+F6)*weight
Units: dmnl

F44component=
    F44*UtilityDplusTminus2
Units: dmnl

F4component=
    F4*UtilityDminusTminus2
Units: dmnl

F5=
    -dTP*estimatedPrevelance*(fracindolent)
Units: dmnl
DzeroTnegative, indolent cases missed by screening

F5component=
    F5*UtilityDzeroTminus2
Units: dmnl

F6=
    -dTP*estimatedPrevelance*(1-fracindolent)
Units: dmnl
D+T-, relevant cases missed by screening

F6component=
    F6*UtilityDplusTminus2
Units: dmnl

FACTORIAL=

EXP(GAMMA LN(5))
Units: dmnl
The GAMMA function is a generalization of the factorial function
        that works on all positive values of X. For an integer N the
        factorial of N is equal to the GAMMA function of N+1. SOURCE:
        http://www.ventanasystems.co.uk/forum/viewtopic.php?f=2&t=4206.

"False Neg Rate (FNR)"[delta]=
        1-"True Pos Rate (TPR)"[delta]
Units: dmnl
False negative rate. False negatives are much less frequent, but
        potentially more serious, because they may result in an
        aggressive malignancy.

"False Pos Rate (FPR)"[delta]=
        1-(NCDF((LnEffThreshold[delta]-"Mu D-")/(2*"Sigma D-")^0.5))
Units: dmnl
False positive rate, also known as the "False positive
        fraction". =P(T+/D-).FPR is defined as the proportion of healthy
        subjects incorrectly classified as diseased. False positives,
        defined as men who are referred for biopsies or other additional
        diagnostic treatments but who are later found not to have tumors
        are clearly the most frequent error.

FINAL TIME = 2040
Units: year
The final time for the simulation.

First PSA Rate=
        First PSA Screening Rate/Number of Tests Per Person/Total Popn*100
Units: 1/year

First PSA Screening Data(
        [(1980,0)-(2000,20)],(1980,0),(1985,0),(1985.9,0),(1986,0.5),(1987,0.5),(1988
,1.75),(1989,3.5),(1990,4),(1991,11),(1992,12.5),(1993,11),(1994,8),(1995,3.5
),(1996,3.5),(1997,3.5),(1998,3.5),(2000,3.5))
Units: 1/year
GET XLS DATA('PSA.xlsx','Sheet1','2', 'L15') does the same thing

First PSA Screening Data Normalized=
        First PSA Screening Data(Time)/27*Max Adoption Fraction
Units: 1/year

First PSA Screening Data Raw:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'B15')
Units: 1/year

First PSA Screening Rate=
        (SUM(Initial Screening TN Rate[Age!])+SUM(Initial Screening FP Rate[Age!])
)*Number of Tests Per Person
Units: tests/year
plus ADD others who developed disease, with 1'st time screening,
        based on constant fraction

First Time FP Rate Per Year[Age]=
        Initial Screening FP Rate[Age]+Screened and FP Rate[Age]
Units: People/year

Formal Threshold=
        Threshold Table(Time)
Units: dmnl

Total PSA using thresholds of 4.0 and 2.5 ng/mL has been used
for screening men.For total PSA values between 4 and 10 ng/mL, a
prostate biopsy is preferred, but lowering the threshold to 2.5
ng/mL has been suggested. Catalona WJ, Loeb S, Han M. Viewpoint:
Expanding prostate cancer screening. Ann Intern Med 144:441-3.
2006. http://www.ncbi.nlm.nih.gov/pubmed/19357513 At this time,
PSA cutoff values (>2.5, 3.0 or 4.0 ng/ml) provide a reasonable
balance between excessive detection rates and the risk of
missing relevant prostate cancer. Men presenting with PSA values
of 2.0-3.0 ng/ml should be reexamined more frequently. 1
Catalona WJ, Smith DS, Ratliff TL, et al. Measurement of
prostate-specific antigen in serum as a screening test for
prostate cancer. N Engl J Med 1991; 324:1156-1161. 2 Catalona
WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with
serum PSA concentrations of 2.6 to 4.0 ng/ml and benign prostate
examination. Enhancement of specificity with free PSA
measurements. JAMA 1997; 277:1452-1455. Several studies have
established the presence of prostate cancer in some men with PSA
levels below 4.0 ng/mL (2), suggesting a need for a more
sensitive test. 2) Catalona WJ, Smith DS, Ornstein DK. Prostate
cancer detection in men with serum PSA concentrations of 2.6 to
4.0 ng/mL and benign prostate examination. Enhancement of
specificity with free PSA measurements. JAMA 1997;277:1452-5. 3)
Punglia RS, D'Amico AV, Catalona WJ, Roehl KA, Kuntz KM.
Effect of verification bias on screening for prostate cancer by
measurement of prostate-specific antigen. N Engl J Med
2003;349:335-42.

FP=
1-"CDF of Threshold for D-"
Units: dmnl
False positive fraction

FP Rate Per Year[Age]=
Nr of FPs Per Person*First Time FP Rate Per Year[Age]
Units: FP/year

fracindolent=
Fract Indolent of Dplus
Units: dmnl

Fract Ever Diagnosed by age[Age]=
ZIDZ(Reported PCa Prevalence or Nr Ever Diagnosed by age[Age],Total Popn by age
[Age])
Units: dmnl
starts with 8-9% increases to 15% after psa screening. SAME
THING AS % PREVALENCE

Fract Ever Had Biopsy=
ZIDZ(SUM(Men Ever Received Biopsy[Age!,Grade!]),Total Popn)
Units: dmnl
I dont know if we have good data but think this is a practically
meaningful variable

Fract Ever Had Biopsy by age[Age]=
ZIDZ(SUM(Men Ever Received Biopsy[Age,Grade!]),Total Popn by age[Age])
Units: dmnl
I dont know if we have good data but think this is a practically
meaningful variable

Fract Indolent of Dplus=

ZIDZ(Total Indolent,Total Dplus)
Units: dmnl

Fract Indolent of Total Popn=
        ZIDZ(Total Indolent,Total Popn)
Units: dmnl

Fract M0 at Detection=
        ZIDZ(dxRateM0,dxRateM0+dxRateM1)
Units: dmnl
Stage distribution at screen detection. out of 100%. increases
                after PSA screening. Etzioni PCSIM model parameter overview- pg.
                13 of 41

Fract M1 at Detection=
        ZIDZ(dxRateM1,dxRateM0+dxRateM1)
Units: dmnl
Stage distribution at clinical presentation. out of 100%.
                increases after PSA screening.

Fract of 35plus Men Popn Living with FP=
        XIDZ(SUM(At Risk and Screened FP[Age!]),Total Popn,0)
Units: dmnl
Fract of 35plus Popn with Progressive Disease=
        Real Progressive PCa Prevalence/Total Popn
Units: dmnl
Etzioni et al., 2008.pg. approximately 40% of popn.

Fract of Clinically Detected=
        1-Fract of PSA Detected
Units: dmnl
out of 100%
Fract of Cost EOL by grade[Grade]=ZIDZ(Cost EOL[Grade],Cost of Treatment by grade[Grade])
Units: dmnl
out of 100%, % cost of treatment

Fract of Cost Init Treatment by grade[Grade]=ZIDZ(SUM(Cost Init Treatment[Grade,Treatment!]),Cost of Treatment by
grade
[Grade])
Units: dmnl
out of 100%, % cost of treatment
Fract of Cost Maintenance by grade[Grade]=
        1-Fract of Cost EOL by grade[Grade]-Fract of Cost Init Treatment by grade[
Grade]
Units: dmnl
out of 100%
Fract of Cost Prevention by grade[Grade]=1-Fract of Cost Treatment by grade[Grade]
Units: dmnl
Fract of Cost Treatment by grade[Grade]=ZIDZ(Cost of Treatment by grade[Grade],Current Cost by grade[Grade])
Units: dmnl
out of 100%
Fract of Distant at Detection by grade[Grade]=
        1-Fract of M0 at Detection by grade[Grade]
Units: dmnl
out of 100%
Fract of Healthy Popn Living with FP=ZIDZ(SUM(At Risk and Screened FP[Age!]),SUM(Total At Risk by age[Age!]))
Units: dmnl
Proportion of D- (healthy) men with a current false positive
                test result. This turn outs to be a really big number if biopsy
                compliance is really that low in the Us when compared to Europe!

242

Fract of Healthy Popn with FP by age[Age]=ZIDZ(At Risk and Screened FP[Age],Total At Risk by age[Age])
Units: dmnl
Proportion of D- (healthy) men with a current false positive
                              test result. This turn outs to be a really big number if biopsy
                              compliance is really that low in the Us when compared to Europe!
Fract of M0 at Detection by grade[Grade]=ZIDZ(dxRateM0 by grade[Grade],(dxRateM0 by grade[Grade]+dxRateM1 by grade[
Grade]))
Units: dmnl
out of 100%. increases after PSA screening.
Fract of M0 at Detection Data:RAW::=
          GET XLS DATA('PSA.xlsx','Sheet1','2', 'G13')
Units: dmnl
Etzioni and Gulati et al. 2008. Med Dec Making. Advanced or
                              metastatic tumors, which in 1980 constituted 25% of newly
                              diagnosed and staged cases, have become a rarity: by 2002, only
                              4% of PCa cases were metastatic at the time of diagnosis. Cowen
                              et al. 1993. 60-65% of the lesions were considered "localized"
                              at the time of diagnosis--ref 85, ref 7. page 18/

Fract of M0 by grade[Grade]=ZIDZ(RealPrevM0 by grade[Grade],(RealPrevM0 by grade[Grade]+RealPrevM1 by grade
[Grade]))
Units: dmnl
percent real prevalence of M0, out of 100%. should be around 80%
Fract of M1 at Detection Data:RAW::=
          GET XLS DATA('PSA.xlsx','Sheet1','2', 'G12')
Units: dmnl
Etzioni and Gulati et al. 2008. Med Dec Making. Advanced or
                              metastatic tumors, which in 1980 constituted 25% of newly
                              diagnosed and staged cases, have become a rarity: by 2002, only
                              4% of PCa cases were metastatic at the time of diagnosis.

Fract of Metastatic deaths of all PCa deaths=ZIDZ(SUM(XXpcM1 by grade[Grade!]),(SUM(XXpcM0 by
grade[Grade!])+SUM(XXpcM1 by grade
[Grade!])))
Units: dmnl

Fract of PCa Deaths of Dplus=ZIDZ(XXpcTotal,XXTotalDplus)
Units: dmnl
% percent of PCa deaths of men with PCa. 40% e.g. means 40% of
                              men with prostate cancer die of prostate cancer, the rest of 60%
                              die of other causes.

Fract of Popn Ever Screened=ZIDZ(SUM(Nr Men Ever Had PSA[Age!]),Total Popn)
Units: dmnl
http://www.ncbi.nlm.nih.gov/pubmed/19821991 FRACT OF POPULATION
                              (HERE 35+ POPN)
Fract of Popn Ever Screened 40s=ZIDZ(SUM(Nr Men Ever Had PSA[AgeGroup40to49!]),SUM(Total Popn by
age[AgeGroup40to49!]))
Units: dmnl
http://www.ncbi.nlm.nih.gov/pubmed/19821991
Fract of Popn Ever Screened 50s=ZIDZ(SUM(Nr Men Ever Had PSA[AgeGroup50to59!]),SUM(Total Popn by
age[AgeGroup50to59!]))
Units: dmnl
http://www.ncbi.nlm.nih.gov/pubmed/19821991
Fract of Popn Ever Screened 60s=(Nr Men Ever Had PSA[AgeGroup60to64]+Nr Men Ever Had PSA[AgeGroup65to69])/
(Total Popn by age[AgeGroup60to64]+Total Popn by age[AgeGroup65to69])
Units: dmnl
http://www.ncbi.nlm.nih.gov/pubmed/19821991
Fract of Popn Ever Screened 70s=ZIDZ(SUM(Nr Men Ever Had PSA[AgeGroup70to79!]),SUM(Total Popn by
age[AgeGroup70to79!]))

Units: dmnl

http://www.ncbi.nlm.nih.gov/pubmed/19821991

Fract of Popn Ever Screened by age[Age]=ZIDZ(Nr Men Ever Had PSA[Age],Total Popn by age[Age])

Units: dmnl

http://www.ncbi.nlm.nih.gov/pubmed/19821991

Fract of Popn Ever Screened over 50=ZIDZ(Nr Men Ever Had PSA over 50,Total Popn above 50)

Units: dmnl

http://www.ncbi.nlm.nih.gov/pubmed/19821991

Fract of Popn Living with FP by age[Age]=XIDZ(At Risk and Screened FP[Age],Total Popn by age[Age],0)

Units: dmnl

Fract of PSA Detected=ZIDZ(sxRateTotal,(sxRateTotal+cxRateTotal))

Units: dmnl

should be around 90%. add ref.

Fract of Real M0=ZIDZ(RealPrevM0,Total Popn)

Units: dmnl

fraction of adult men population with M0

fract of real M0 to real M1=ZIDZ(Total M0,(Total M0+Total M1))

Units: dmnl

Fract of Real M1=ZIDZ(RealPrevM1,Total Popn)

Units: dmnl

fraction of adult men population with M1

Fract of Real PCa Prevalence=Real PCa Prevalence/Total Popn

Units: dmnl

fraction of population with PCa

Fract of Real PCa Prevalence by age[Age]=ZIDZ(Real PCa Prevalence by age[Age],Total Popn by age[Age])

Units: dmnl

not over the whole population, but over the D+ population.

Fract of Real PCa Prevalence by grade[Grade]=Real PCa Prevalence by grade[Grade]/Total Popn

Units: dmnl

the sum of these percentages gives the % of the pca in the whole
                population, cannot be divided to pop(grade), doesnt exist

Fract of Reported PCa Prevalence=ZIDZ(Reported PCa Prevalence,Total Popn)

Units: dmnl

Includes indolent disease, as we dont know if it was indolent or
                not. 1.38e+007 in 2010. Assuming constant incidence, survival,
                and cost, projection is 13.8 and 18.1 million cancer survivors
                in 2010 and 2020, respectively, with associated costs of cancer
                care of 124.57 and 157.77 billion 2010 US dollars.
                http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
                survivor: any person diagnosed with cancer, from the time of
                initial diagnosis until his or her death.
                http://costprojections.cancer.gov/cancer.prevalance.htm

Fract of Reported Prevalence or ever diagnosed=
         ZIDZ(SUM(Reported PCa Prevalence or Nr Ever Diagnosed by age[Age!]),Total Popn)

Units: dmnl

Starts with 8-9% increases to 15% after psa screening. SAME
                THING AS % PREVALENCE. Lifetime Risk of Developing Cancer:
                Approximately 15.0 percent of men will be diagnosed with
                prostate cancer at some point during their lifetime, based on
                2009-2011 data.

Fract of Unnecessary Biopsies by age[Age]=ZIDZ(Unnecessary Biopsy Rate by age[Age],Biopsy Rate by age[Age])

Units: dmnl

Fract Real M0=RealPrevM0/Total Popn

Units: dmnl

fract of real M0, as another variable?

Fract Real M1=RealPrevM1/Total Popn

Units: dmnl

Fract Receiving RP M1Low=1

Units: dmnl

Fract Receiving RT M1Low=1

Units: dmnl

Fract Reported PCa Prevalence by age[Age]=ZIDZ(SUM("Reported PCa Prevalence (Nr Ever Diagnosed) by age grade"[Age,Grade!]),Total Popn by age[Age])
Units: dmnl
Percent of men ever received a diagnosis, ever diagnosed..this number increased from 8 to 15% from 1985 to... out of 100%
Fract Treated=ZIDZ(Treated Total,Total Popn)
Units: dmnl
should reach 40% by 2020-2025? check background slide, add ref.
Fract Treated by age[Age]=ZIDZ(Nr Treated by age[Age],Total Popn by age[Age])
Units: dmnl
should reach 40% by 2020-2025? check background slide, add ref.
		1.38e+007 in 2010. Assuming constant incidence, survival, and
		cost, projection is 13.8 and 18.1 million cancer survivors in
		2010 and 2020, respectively, with associated costs of cancer
		care of 124.57 and 157.77 billion 2010 US dollars.
		http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
		survivor: any person diagnosed with cancer, from the time of
		initial diagnosis until his or her death.
		http://costprojections.cancer.gov/cancer.prevalance.html
Fract Treated by grade[Grade]=ZIDZ(Nr Treated by grade[Grade],Total Popn)
Units: dmnl
should reach 40% by 2020-2025? check background slide, add ref.
		1.38e+007 in 2010. Assuming constant incidence, survival, and
		cost, projection is 13.8 and 18.1 million cancer survivors in
		2010 and 2020, respectively, with associated costs of cancer
		care of 124.57 and 157.77 billion 2010 US dollars.
		http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
		survivor: any person diagnosed with cancer, from the time of
		initial diagnosis until his or her death.
		http://costprojections.cancer.gov/cancer.prevalance.html
Fract Treated by grade treatment[Grade,Treatment]=
	ZIDZ(SUM(Nr Treated by age grade treatment[Age!,Grade,Treatment]),Total Popn)
Units: dmnl
Cancer survivor: any person diagnosed with cancer, from the time
		of initial diagnosis until his or her death. Assuming constant
		incidence, survival, and cost, projection is 13.8 and 18.1
		million cancer survivors in 2010 and 2020, respectively, with
		associated costs of cancer care of 124.57 and 157.77 billion
		2010 US dollars.
		http://jnci.oxfordjournals.org/content/103/2/117.long.
		http://costprojections.cancer.gov/cancer.prevalance.html
Fract Treated by treatment[Treatment]=ZIDZ(Nr Treated by treatment[Treatment],Total Popn)
Units: dmnl
Cancer survivor: any person diagnosed with cancer, from the time
		of initial diagnosis until his or her death. Assuming constant
		incidence, survival, and cost, projection is 13.8 and 18.1
		million cancer survivors in 2010 and 2020, respectively, with
		associated costs of cancer care of 124.57 and 157.77 billion
		2010 US dollars.
Fraction Ever Diagnosed 40s=SUM(Fract Ever Diagnosed by age[AgeGroup40to49!]*Total Popn by age[AgeGroup40to49 !])/SUM(Total Popn by age[AgeGroup40to49!])
Units: dmnl
Fraction Ever Diagnosed 50s=SUM(Fract Ever Diagnosed by age[AgeGroup50to59!]*Total Popn by age[AgeGroup50to59 !])/SUM(Total Popn by age[AgeGroup50to59!])
Units: dmnl
Fraction Ever Diagnosed 60s=SUM(Fract Ever Diagnosed by age[AgeGroup60to69!]*Total Popn by age[AgeGroup60to69 !])/SUM(Total Popn by age[AgeGroup60to69!])
Units: dmnl
Fraction Ever Diagnosed 70s=SUM(Fract Ever Diagnosed by age[AgeGroup70to79!]*Total Popn by age[AgeGroup70to79 !])/SUM(Total Popn by age[AgeGroup70to79!])
Units: dmnl

Fraction Experiencing Harms=Max Fraction Experiencing Harms*Eff of T on Harms
Units: dmnl
Fraction F=0
Units: dmnl
Fraction getting screenings after diagnosis
Fraction of HR Industry Revenue Allocated to RD=0.2
Units: dmnl
Fraction of Harm reduction industry revenue for R&D Table
    function for RD(Marginal Return to RD)
Fraction of Onset Nonprogressive Type= 0.3
Units: dmnl
80% of disease is of non-progressive type. Greater than 80% of
    men with newly diagnosed cancers have local or regional stage
    disease (Ries et al., Nat. Cancer Inst. 2002) and the majority
    of men with clinically localized cancer are offered aggressive
    treatment with radical prostatectomy (RP) or radiation therapy
    (RT) (Fowler and Collins et al., JAMA,2000). The use of RP has
    increased substantially during 1990's (Lu-Yao and Friedman et
    al., 1997, Mettlin, 1997) from (Hoffman et al., 2003)
Fraction of undiagnosed disease discovered at time of death=1
Units: dmnl
Fractions may be different for M0 vs. M1 disease. fM1>fM0.
    subscript by M0 m1?? How about Attribution Bias: incorrect
    labeling of death from other causes as death from PCa (Feuer et
    al., JNCI, 1999)
Fractional Improvement in Technology=Ref Yield to RD*R and D
Units: 1/year
fractional improvement in technology, or Gamma
fractrealprev=ZIDZ(RealPrev,Total Popn)
Units: dmnl
Ftotal=F1+F2+F3+F4+F5+F6
Units: dmnl
goldman 2005=1
Units: dmnl
Treatment rates would vary by the type of cancer andwhether it
    has metastasized (Exhibit 6). Half of patients with local
    disease would get treatment (21 percent of all cancer patients);
    100 percent of patientswith disseminated disease (41 percent of
    cancer patients) and 100 percent of patients with other cancers
    (18 percent of cancer patients) would get treatment.
Grade:High,Low,Latent
High Grade, Low Grade, or Latent (Indolent) tumor
group:prof,advoc
Guideline Start Year[group]=1985
Units: year
HARMS[group]=SUM(Unit Cost[group,testoutcome!,diseasestate!]*Probability of Test Outcome
[testoutcome!,diseasestate!])
Units: dmnl
Total amount of harms for screening
Harms of Treatment=1
Units: dmnl
Risks of therapy--Even in the absence of treatment, many men
    found to have prostate cancer as a result of screening will have
    a lengthy period of time without clinical problems. However,
    undergoing radical prostatectomy and radiation therapies can
    lead to immediate complications:
Harms to Benefits Ratio[group]=ZIDZ(HARMS[group],BENEFITS[group])
Units: dmnl
"Harms to Benefits Ratio". It represents the real/actual ratio of harms to benefits of screening.
"Hazard of non-PCa death"=1
Units: 1/year

Hazard of non-PCa death
Hazard Ratios Associated with Initial Treatments CM RP RT=1
Units: 1/year
Hazard Ratios Associated with Initial Treatments, i.e.
                Conservative Management CM, Radical Prostatectomy RP, RT,
                Radiation Therapy, or RT combined with Hormones
HazardAsxOnset[Age]=0,0.0004,0.0025,0.003,0.005,0.01,0.015,0.025,0.03,0.05
        {hazard of disease onset: etzioni and cowen, 1999, creates carter prevalence curve}
Units: 1/year
0.001098,0.001604,0.002376, 0.003535,0.005346,
                0.008327,0.013039, 0.020303,0.031163, 0.04949--cowen 1999
                0,0.0004,0.0025,0.003,0.005,0.01,0.015,0.025,0.03,0.05
                0.001098,0.0002,0.0002,0.00151,0.00151,0.00243,0.00243,0.00522,0.
                00522,0.00712--?
                0,0.0004,0.0025,0.003,0.005,0.01,0.015,0.025,0.03,0.05--calibrati
                on to incidence by age Etzioni et al., 1999- Table 1.
                http://www.ncbi.nlm.nih.gov/pubmed/10458357 Bubendorf et al in
                Underwood, 2012, Table 9 gives lower and upper bounds:
                http://www.ncbi.nlm.nih.gov/pubmed/22302420
HBR For Action[group]=IF THEN ELSE(Pseudo HBR[group]>1,Max(HBRMinSignal+1,Pseudo HBR[group]),Min
(1-HBRMinSignal,Pseudo HBR[group]))
Units: dmnl
HBR Multiplier[group]=0.3,0.3;
Units: dmnl
Multiplier for the effect of HBR on starting age of screening.
HBR Reference=1
Units: dmnl
HBR Trans Delay=4
Units: year
Scientific evidence translation delay Time constant for the HBR (harms to benefits ratio) perception delay
HBRMinSignal=0.1
Units: dmnl
Units: dmnl
Empirical evidence from these types of studies suggests that
                medical technology accounts for about 10 to 40 percent of the
                increase in health care expenditures over time
HR Revenue=Avg Price Per HRT*HRT Rate per year
Units: $/year
HRT Per Person Per Year=0.025
Units: procedure/person/year
Harm reduction treatment per person per year, constant. assume
                po an average they use 1 piece of technology per 40 years
HRT Rate per year=HRT Per Person Per Year*Pop Eligible for HRT
Units: procedure/year
PCa Diagnosed(Time)*Treatment Per Diagnosed Cancer+PCa Survivors(Time)*Treatment Per Diagnosed Cancer *Relative
Treatment Rate of Survivors
Treatment induced deaths, Feuer et al., 1999
Imm At Risk[AgeUnder65]=NetImRate Data*At Risk Never Screened Pop[AgeUnder65]
Imm At Risk[Age65Plus]=0
        Units: People/year
ImmAtRiskFP[AgeUnder65]=NetImRate Data*At Risk and Screened FP[AgeUnder65]
ImmAtRiskFP[Age65Plus]=0
        Units: People/year
        Adult net immigration rate*At Risk and Screened FP[Age]
ImmAtRiskTN[AgeUnder65]=
        NetImRate Data*At Risk and Screened TN[AgeUnder65]
ImmAtRiskTN[Age65Plus]=0
        Units: People/year
        Adult net immigration rate*At Risk and Screened TN[Age]
ImmCxM0[Age,Grade]=NetImRate Data*Cx LocoRegional M0[Age,Grade]
Units: People/year

Adult net immigration rate*Cx LocoRegional M0[Age,Grade]
ImmCxM1[AgeUnder65,Grade]=NetImRate Data*Cx Distant M1[AgeUnder65,Grade]
ImmCxM1[Age65Plus,Grade]=0
        Units: People/year
        Adult net immigration rate*Cx Distant M1[Age,Grade]
ImmSwitch=1
Units: dmnl
ImmSxM0[AgeUnder65,Grade]=NetImRate Data*Sx LocoRegional M0[AgeUnder65,Grade]
ImmSxM0[Age65Plus,Grade]=0
        Units: People/year
        Adult net immigration rate*Sx LocoRegional M0[Age,Grade]
ImmSxM1[AgeUnder65,Grade]=NetImRate Data*Sx Distant M1[AgeUnder65,Grade]
ImmSxM1[Age65Plus,Grade]=0
        Units: People/year
        Adult net immigration rate*Sx Distant M1[Age,Grade]
ImmTxCxM0[AgeUnder65,Grade,Treatment]=NetImRate Data*Tx CxM0[AgeUnder65,Grade,Treatment]
ImmTxCxM0[Age65Plus,Grade,Treatment]=0
        Units: People/year
        Adult net immigration rate*Tx CxM0[Age,Grade,Treatment]
ImmTxCxM0M1[AgeUnder65,Grade,Treatment]=NetImRate Data*Tx CxM0M1[AgeUnder65,Grade,Treatment]
ImmTxCxM0M1[Age65Plus,Grade,Treatment]=0
        Units: People/year
        Adult net immigration rate*Tx CxM0M1[Age,Grade,Treatment]
ImmTxCxM1[AgeUnder65,Grade,Treatment]=NetImRate Data*Tx CxM1[AgeUnder65,Grade,Treatment]
ImmTxCxM1[Age65Plus,Grade,Treatment]=0
        Units: People/year
        Adult net immigration rate*Tx CxM1[Age,Grade,Treatment]
ImmTxSxM0[AgeUnder65,Grade,Treatment]=NetImRate Data*Tx SxM0[AgeUnder65,Grade,Treatment]
ImmTxSxM0[Age65Plus,Grade,Treatment]=0
        Units: People/year
        Adult net immigration rate*Tx SxM0[Age,Grade,Treatment]
ImmTxSxM0M1[AgeUnder65,Grade,Treatment]=NetImRate Data*Tx SxM0M1[AgeUnder65,Grade,Treatment]
ImmTxSxM0M1[Age65Plus,Grade,Treatment]=0
        Units: People/year
        Adult net immigration rate*Tx SxM0M1[Age,Grade,Treatment]
ImmTxSxM1[AgeUnder65,Grade,Treatment]=NetImRate Data*Tx SxM1[AgeUnder65,Grade,Treatment]
ImmTxSxM1[Age65Plus,Grade,Treatment]=0
        Units: People/year
        Adult net immigration rate*Tx SxM1[Age,Grade,Treatment]
ImmUxM0[AgeUnder65,Grade]=NetImRate Data*Ux LocoRegional M0[AgeUnder65,Grade]
ImmUxM0[Age65Plus,Grade]=0
        Units: People/year
        Adult net immigration rate*Ux LocoRegional M0[Age,Grade]
ImmUxM1[AgeUnder65,Grade]=NetImRate Data*Ux Distant M1[AgeUnder65,Grade]
ImmUxM1[Age65Plus,Grade]=0
        Units: People/year
        Adult net immigration rate*Ux Distant M1[Age,Grade]
Incidence ALL=
        IF THEN ELSE(Time<2010,Incidence All per 100thou, 0)
Units: People/year
Incidence All per 100thou=
        Reported PCa Incidence/Total Popn Time Series ALL AGES*per100000men
Units: People/year
Incidence and Mortality=1
Units: dmnl
United States cancer statistics: 1999-2012 cancer incidence and
                mortality data. US Dept of Health and Human Services.
                https://nccd.cdc.gov/uscs/. Accessed October 22, 2015
                https://nccd.cdc.gov/uscs/
Incidence Per 100thou=Total Popn Incidence Rate*per100000men
Units: People/year

Indicated Starting Age for Screening[group]=Actual Starting Age for Routine Screening*Effect of HBR on Indicated Age for
Screening
[group]
Units: Ages
Init Age Distr[Age]=
        0.0003103,0.0006117,0.0032613,0.0101715,0.0232526,0.0479957,0.0884139,0.164051
,0.171615,0.490317
Units: dmnl
0.0003103,0.0006117,0.0032613,0.0101715,0.0232526,0.0479957,0.088
        4139,0.164051,0.171615,0.490317

Init Age in Years=35
Units: year
Init Fract Dplus[Age]=
        0,0.00177,0.01184,0.02107,0.03569,0.06435,0.1016,0.1563,0.2072,0.3713
Units: dmnl
0.005,0.01,0.02,0.03,0.05,0.08,0.13,0.19,0.27,0.46
        0,0.00177,0.01184,0.02107,0.03569,0.06435,0.1016,0.1563,0.2072,0.
        3713 (1-this fraction) gives the fraction of D- of the
        population (above 35 years and older?) subscript by age group,
        also grade? initialize: no screening, real prevalence by
        age--steady state

Init Fract DxTxM0=0.87
Units: dmnl
1-this fraction gives the fraction of diagnosed and treated M0's
Init Fract DxTxM1=0.83
Units: dmnl
1-this fraction gives the fraction of diagnosed and treated M1's 0.9
Init Fract Indolent of DPlus=1
Units: dmnl
Init Fract M0[Grade]=
        0.9,0.99,1
Units: dmnl
(1-this fraction) gives M1. Indolent does not progress to M1. Localized 0.96, regional 0.01, distant 0.03
Init Fract M0 at Detection=0.75
Units: dmnl
Init Fract UxM0=0.75
Units: dmnl
(1- this fraction of M0) is diagnosed (and treated or untreated
        yet). this might be important as this fraction will be much
        bigger before screening starts
Init Fract UxM1=0.55
Units: dmnl
(1- this fraction of M1) is diagnosed (and treated or untreated
        yet). this might also be important as this fraction will be a
        bit bigger before screening starts
Init Grade[Grade]=0.05,0.65,0.3
Units: dmnl
0.333333,0.333333,0.333333 0.15,1.35,1.5
INIT R[group]=40,40
Units: Ages
Initial recommended starting age
Init Technology=0.2
Units: dmnl
INIT Threshold[group]=4,4;
Units: dmnl
Set of initial values of the Threshold T for different groups 0.5,0.5;
Initial Prevalence[Age]=
        0
Units: People

Initial Screening FN Rate[Age,Grade]=
  Ux LocoRegional M0[Age,Grade]/TimeBtwSx*"P(T-/D+)"*Screen Switch
Units: People/year
doesnt exist, since they are all true negatives. john: fraction
        of False negatives (P(T-/D+) to never screened. there is no
        never screened, everybody gets screened (except first flow,
        Asxinci?). ask again.

Initial Screening FP Rate[Age]=
  At Risk Never Screened Pop[Age]/AvgTimetoVisit*(1-Specificity)*Current Screened Fraction
[Age]*Screen Switch
Units: People/year

Initial Screening TN Rate[Age]=
  At Risk Never Screened Pop[Age]/AvgTimetoVisit*PofTminusDminus*Current Screened Fraction
[Age]*Screen Switch
Units: People/year

INITIAL TIME = 1980
Units: year
The initial time for the simulation.

InitialHBRBias[group]=
  -0.2,-0.8
Units: dmnl

Innovation to Reduce Harms=
  Technology T*(Tmax-Technology T)*Fractional Improvement in Technology
Units: 1/year
innovation to reduce harms, or rate of change in T

Instantaneous Biopsy Disutility=
  0.02
Units: dmnl
unit= Utility/Biopsies? One time utility decrement associated
        with prostate biopsy. from Underwood et al., 2012--0.01 to 0.1.
        Simulation optimization of PSA-threshold based prostate cancer
        screening policies. http://www.ncbi.nlm.nih.gov/pubmed/22302420
        Chhatwal, Alagoz et al., 2010. Optimal Breast Biopsy
        Decision-Making Based on Mammographic Features and Demographic
        Factors:
        http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3057079/http://www.nc
        bi.nlm.nih.gov/pmc/articles/PMC3057079/

Last Year of Life Cost oc Death=
  62242
Units: $/person
last year, one time cost of a PCa patient (?) who dies of other
        causes

Last Year of Life Cost PCa Death=
  Base Last Year of Life Cost PCa Death*Table Eff of T on Cost of Treatment(
Technology T)
Units: $/person

Lead Time=
  10
Units: year
The amount of time that diagnosis is moved forward by the test
        (Yao and Yao, 2002). Lead-time is included as a survival benefit

for CISNET models:
https://resources.cisnet.cancer.gov/registry/glossary/#assumption
sbenefit-factorsscreeninglead-time Lead times estimates vary
depending on the methods and definitions, but estimates of 8-12
years are well founded. Hence, the follow-up period of trials in
the PSA era must be at least 8-12 years just to get to the
median point at which cases would have been diagnosed in the
pre-PSA era. Source, 2015:
ttp://onlinelibrary.wiley.com/doi/10.1002/ijc.29408/epdf.
Average lead time estimates can be found in Telesca et al
Draisma et al estmated higher lead times of 11.6 years for PSA
screning for men aged 55-75 years. PCSIM PAGE LEAD TIME 22-6.8
MEAN, SOJOURN TIME 8.6 MEAN, AGE ADJUSTED

Lead Time Bias due to Screening=
        4.92
Units: dmnl
Weighted to US race distribution - 4.59 yrs * 85% White + 6.78
                yrs * 15% Black/Other = 4.92 yrs

Lead time in M0=
        4.92
Units: dmnl
Weighted to US race distribution - 4.59 yrs * 85% White + 6.78
                yrs * 15% Black/Other = 4.92 yrs

Lead time in M1=
        1
Units: dmnl

LeaveAge[AgeUnder80]=
        At Risk Never Screened Pop[AgeUnder80]/Years Per Cohort*Aging Switch
LeaveAge[Age80Plus]=
                0
        Units: People/year
        Rate of leaving from the indicated age category. This rate is
                        zero for the last age category, 80+, as they dont leave the age
                        group.

LeaveAgeCxM0[AgeUnder80,Grade]=
        Cx LocoRegional M0[AgeUnder80,Grade]/Years Per Cohort*Aging Switch
LeaveAgeCxM0[Age80Plus,Grade]=
                0
        Units: People/year

LeaveAgeCxM1[AgeUnder80,Grade]=
        Cx Distant M1[AgeUnder80,Grade]/Years Per Cohort*Aging Switch
LeaveAgeCxM1[Age80Plus,Grade]=
                0
        Units: People/year

LeaveAgeFP[AgeUnder80]=
        At Risk and Screened FP[AgeUnder80]/Years Per Cohort*Aging Switch
LeaveAgeFP[Age80Plus]=
                0
        Units: People/year

LeaveAgeSxM0[AgeUnder80,Grade]=
        Sx LocoRegional M0[AgeUnder80,Grade]/Years Per Cohort*Aging Switch
LeaveAgeSxM0[Age80Plus,Grade]=
                0

251

Units: People/year

LeaveAgeSxM1[AgeUnder80,Grade]=
　　　Sx Distant M1[AgeUnder80,Grade]/Years Per Cohort*Aging Switch
LeaveAgeSxM1[Age80Plus,Grade]=
　　　　　　0
　　　Units: People/year

LeaveAgeTN[AgeUnder80]=
　　　At Risk and Screened TN[AgeUnder80]/Years Per Cohort*Aging Switch
LeaveAgeTN[Age80Plus]=
　　　　　　0
　　　Units: People/year

LeaveAgeTxCxM0[AgeUnder80,Grade,Treatment]=
　　　Tx CxM0[AgeUnder80,Grade,Treatment]/Years Per Cohort*Aging Switch
LeaveAgeTxCxM0[Age80Plus,Grade,Treatment]=
　　　　　　0
　　　Units: People/year

LeaveAgeTxCxM0M1[AgeUnder80,Grade,Treatment]=
　　　Tx CxM0M1[AgeUnder80,Grade,Treatment]/Years Per Cohort*Aging Switch
LeaveAgeTxCxM0M1[Age80Plus,Grade,Treatment]=
　　　　　　0
　　　Units: People/year

LeaveAgeTxCxM1[AgeUnder80,Grade,Treatment]=
　　　Tx CxM1[AgeUnder80,Grade,Treatment]/Years Per Cohort*Aging Switch
LeaveAgeTxCxM1[Age80Plus,Grade,Treatment]=
　　　　　　0
　　　Units: People/year

LeaveAgeTxSxM0[AgeUnder80,Grade,Treatment]=
　　　Tx SxM0[AgeUnder80,Grade,Treatment]/Years Per Cohort*Aging Switch
LeaveAgeTxSxM0[Age80Plus,Grade,Treatment]=
　　　　　　0
　　　Units: People/year
　　　MISTAKE: SUM(Tx SxM0[Age,Grade!,Treatment!])/Years Per Cohort

LeaveAgeTxSxM0M1[AgeUnder80,Grade,Treatment]=
　　　Tx SxM0M1[AgeUnder80,Grade,Treatment]/Years Per Cohort*Aging Switch
LeaveAgeTxSxM0M1[Age80Plus,Grade,Treatment]=
　　　　　　0
　　　Units: People/year

LeaveAgeTxSxM1[AgeUnder80,Grade,Treatment]=
　　　Tx SxM1[AgeUnder80,Grade,Treatment]/Years Per Cohort*Aging Switch
LeaveAgeTxSxM1[Age80Plus,Grade,Treatment]=
　　　　　　0
　　　Units: People/year

LeaveAgeUxM0[AgeUnder80,Grade]=
　　　Ux LocoRegional M0[AgeUnder80,Grade]/Years Per Cohort*Aging Switch
LeaveAgeUxM0[Age80Plus,Grade]=
　　　　　　0
　　　Units: People/year

LeaveAgeUxM1[AgeUnder80,Grade]=
　　　Ux Distant M1[AgeUnder80,Grade]/Years Per Cohort*Aging Switch
LeaveAgeUxM1[Age80Plus,Grade]=
　　　　　　0

252

Units: People/year

LeaveTreatCxM0[Age,Grade,Treatment,TreatmentTo]=
        Tx CxM0[Age,Grade,Treatment]*pChgTxM0[Treatment,TreatmentTo]*Treatment Switch
Units: People/year

LeaveTreatCxM0M1[Age,Grade,Treatment,TreatmentTo]=
        Tx CxM0M1[Age,Grade,Treatment]*pChgTxM0[Treatment,TreatmentTo]*Treatment Switch
Units: People/year

LeaveTreatCxM1[Age,Grade,Treatment,TreatmentTo]=
        Tx CxM1[Age,Grade,Treatment]*pChgTxM1[Treatment,TreatmentTo]*Treatment Switch
Units: People/year

LeaveTreatSxM0[Age,Grade,Treatment,TreatmentTo]=
        Tx SxM0[Age,Grade,Treatment]*pChgTxM0[Treatment,TreatmentTo]*Treatment Switch
Units: People/year

LeaveTreatSxM0M1[Age,Grade,Treatment,TreatmentTo]=
        Tx SxM0M1[Age,Grade,Treatment]*pChgTxM0[Treatment,TreatmentTo]*Treatment Switch
Units: People/year

LeaveTreatSxM1[Age,Grade,Treatment,TreatmentTo]=
        Tx SxM1[Age,Grade,Treatment]*pChgTxM1[Treatment,TreatmentTo]*Treatment Switch
Units: People/year

Lifetime Risk of Dying of PCa=
        ZIDZ(XXpcTotal,(XXocTotal+XXpcTotal))*100
Units: dmnl
objective, or actual risk of death from PCa with correct initial
                values for the simulation, this wont change much, probably from
                3% to 2.5%s only.

Lifetime Risk of Getting a Diagnosis=
        (XXocTotal+XXpcTotal-XXUndiagnosed)/(XXocTotal+XXpcTotal)*100
Units: dmnl
Lifetime risk of getting a diagnosis of PCa, changes between
                0-100 Increased from 8% to over 15% after PSA

Likelihood Biopsy Referral=
        1
Units: dmnl
Likelihood of referral to biopsy if PSA is below 4 ng/ml. The
                frequency of referral to biopsy among men with PSA below 4 ng/ml
                id based on a study by Schroder et al (1998) which found that
                the sensitivity of DRE is approximately 20% for PSA below 3
                ng/ml and 40% for PSA from 3.0 t0 3.9 ng/ml. (Schroder et al.,
                1998)

LnEffThreshold[d1]=
        LN(Effective Threshold)
LnEffThreshold[d2]=
                LN(Effective Threshold+tdelta)
        Units: dmnl

LnX=
        LN(Cutoff X)
Units: dmnl
Natural logarithm of the Cutoff value X. See Inoue an Etzioni et
                al., 2004. LN(Cutoff X+1)

Local vs US multiplier on popn death rate=
    1
Units: dmnl

M T distribution=
    1
Units: dmnl
M0,T1 42.16 M0,T2 29.87 M0,T3 20.76, total M0= 92.79 M1,T1 0
        M1,T2 2.75 M1,T3 4.45, total M1= 7.11

M0 OC death rate by age[Age]=
    ZIDZ(SUM(XXocLocoReg[Age,Grade!]),SUM(Total M0 by age grade[Age,Grade!]))
Units: 1/year

M0 PC death rate by age[Age]=
    ZIDZ(SUM(XXpcM0 by age grade[Age,Grade!]),SUM(Total M0 by age grade[Age,Grade
!]))
Units: 1/year

M1 OC death rate by age[Age]=
    ZIDZ(SUM(XXocDistant[Age,Grade!]),SUM(Total M1 by age grade[Age,Grade!]))
Units: 1/year

M1 PC death rate by age[Age]=
    ZIDZ(SUM(XXpcM1 by age grade[Age,Grade!]),SUM(Total M1 by age grade[Age,Grade
!]))
Units: 1/year

Male Pop Turning 35[AgeGroup35to39]=
        Adult men popn millions turning 35 time series Data
Male Pop Turning 35[AgeGroup40to44]=
            0
Male Pop Turning 35[AgeGroup45to49]=
            0
Male Pop Turning 35[AgeGroup50to54]=
            0
Male Pop Turning 35[AgeGroup55to59]=
            0
Male Pop Turning 35[AgeGroup60to64]=
            0
Male Pop Turning 35[AgeGroup65to69]=
            0
Male Pop Turning 35[AgeGroup70to74]=
            0
Male Pop Turning 35[AgeGroup75to79]=
            0
Male Pop Turning 35[AgeGroup80plus]=
                0
        Units: People/year
        Pop Increase Time Series(Time), subscript by age group THE ONLY
                        INFLOW, 1.5e+006

Marginal Return to RD=
        dTdRandD
Units: 1/$
dTdRandD

"Marginal Subst Rate (MSR)"=
        "True Pos Rate (TPR)"[d1]/"False Pos Rate (FPR)"[d1]
Units: dmnl
TPR/FPR. A small increase in the selection rate would result in

254

about MSR times additional false positives for every true positive added. Marginal Substitution Rate- Stewart, 2008. The rate at which false positives are substituted for true positives at a given selection. rate is called the marginal substitution rate. The optimal selection rate is found when the marginal substitution rate equals the ratio of the benefit of a true positive to the cost of a false positive. The optimal selection rate depends on the benefits of true positives (e.g., the health benefits of early detection and treatment) and true negatives (e.g., the psychological benefits of correct disease-free diagnoses) and the costs of false positives (e.g., costly and painful biopsies and other diagnostic treatments of healthy women) and false negatives (e.g., all the costs associated with failure to treat non-detected tumors). The imputed marginal rate of substitution for this case is 32.8. A small increase in the selection rate would result in about 33 additional false positives for every true positive added. If this ratio is unacceptable, then the selection rate should not be increased and consideration might be given to decreasing it. This doctor is behaving as if 33 were the ideal substitution rate. This would be optimal if the benefit of an additional true positive were 33 times greater than the cost of a false positive. We will not argue whether this benefit-cost ratio is correct or incorrect, because that is not a technical matter. The substitution rate is, however, a meaningful number, and informed social policy

Max Adoption Fraction=
        0.75
Units: dmnl
Maximum fraction of doctors adopting the practice

Max Fraction Experiencing Harms=
        0.9
Units: dmnl

Mean age at Cx=
        ZIDZ(SUM(AgeGpMean[Age!]*cxRatePCa by age[Age!]),SUM(cxRatePCa by age[Age!]))
Units: Ages

Mean age at Death=
        ZIDZ(SUM(AgeGpMean[Age!]*XXTotalbyAge[Age!]),SUM(XXTotalbyAge[Age!]))
Units: Ages
incorrect, popn below 35 is missing--no comparison

Mean Age at Death Data:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','NP2014-T17','3', 'B16')
Units: dmnl
Prostate cancer: mean age at death from CENSUS data for male

Mean age at Death M0=
        ZIDZ(SUM(AgeGpMean[Age!]*XXpcM0 by age[Age!]),SUM(XXpcM0 by age[Age!]))
Units: Ages

Mean age at Death M1=
        ZIDZ(SUM(AgeGpMean[Age!]*XXpcM1 by age[Age!]),SUM(XXpcM1 by age[Age!]))
Units: Ages

Mean age at Dx=
        ZIDZ(SUM(AgeGpMean[Age!]*dxRatePCa by age[Age!]),SUM(dxRatePCa by age[Age!]

]))
Units: Ages

Mean Age at Dx Data:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G8')
Units: dmnl
Prostate cancer: not just your grandfather's disease by denise
                pierce- mean age at initial diagnosis World bank data --mean age
                at death

Mean Age at Initial Dx for PCa Data:=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'C8')
Units: dmnl
Table 2. Mean Age at Initial Diagnosis for Prostate Cancer:
                chrome-extension://oemmndcbldboiebfnladdacbdfmadadm/http://www.ni
                ahealthcare.com/media/475200/final%20layout_mco-regulatory%20&%20
                reimbursement_q1-12.pdf

Mean age at PCa Death=
        ZIDZ(SUM(AgeGpMean[Age!]*XXpc by age[Age!]),SUM(XXpc by age[Age!]))
Units: Ages

Mean age at Sx=
        ZIDZ(SUM(AgeGpMean[Age!]*sxRatePCa by age[Age!]),SUM(sxRatePCa by age[Age!
]))
Units: Ages

Mean Age Data=
        SUM(AgeGpMean[Age!]*Adult men popn counts time series[Age!])/Adult men popn count TOTAL
Units: Ages

Mean Age Data 1980to2014=
        (40*Pop Time Series 35to44+50*Pop Time Series 45to54+60*Pop Time Series 55to64
+70*Pop Time Series 65to74+80*Pop Time Series 75to84+88*Pop Time Series 85plus
)/Total Popn Time Series 1979to2014
Units: dmnl

Mean Age Data1980to2014:=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G83')
Units: dmnl

Mean Age Simulation=
        SUM(AgeGpMean[Age!]*Total Popn by age[Age!])/Total Popn
Units: Ages

Mean Cohort Size=
        5
Units: year

"mean D+"=
        EXP("Mu D+"+"Sigma D+"^2/2)
Units: dmnl
LN("Mu D+")-"Sigma D+"^2/2

"mean D-"=
        EXP("Mu D-"+"Sigma D-"^2/2)
Units: dmnl
LN("Mu D-")-"Sigma D-"^2/2

"Mean PSA Etzioni, 2004"=
        1.84

Units: ng/ml
Etzioni et al., 2014. Cancer Epidemiology and Biomarkers.
                    http://www.ncbi.nlm.nih.gov/pubmed/15466981 Mean PSA is 1.84
                    ng/ml, at mean age 60. 5.50 ng/ml for cancer patients?

Mean Sojourn Time=
                    1/Progression rate of undiagnosed disease
Units: year
The duration of the preclinical stage in the absence of
                    screening (a random variable) is termed sojourn time. It
                    represents the potential time from tumor onset to its clinical
                    diagnosis. Weibull distribution with mean and shape parameter
                    for baseline sojourn time hazard. Sojourn time = f(age, secular
                    trend). Estimate and distribution is in Tsodikov et al., 2006 a
                    population model of prostate cancer incidence. etzioni et al
                    1998; gulati et al, 2010 page 714-715 sojourn time is given by
                    age groups.

Mean Time from Test to Diagnosis=
                    8.57/12
Units: year
Etzioni et al, 2004. http://www.ncbi.nlm.nih.gov/pubmed/15466981

"median D+"=
                    EXP("Mu D+")
Units: dmnl
LN("Mu D+")-"Sigma D+"^2/2

"median D-"=
                    EXP("Mu D-")
Units: dmnl
LN("Mu D-")-"Sigma D-"^2/2

Medicare Claim Procedure Codes for PSA test=
                    1
                    {Prostate specific antigen (PSA) Screening Code: G0103, Diagnostic Code: 86316 (prior to 1988), 84153(1988
and later)
                    Digital rectal examination (DRE) Screening Code: G0102.   Procedure Codes for SEER-Medicare
Analyses.}
Units: dmnl
http://healthcaredelivery.cancer.gov/seermedicare/considerations/
                    procedure_codes.html Prostate specific antigen (PSA) Screening
                    Code: G0103, Diagnostic Code: 86316 (prior to 1988),84153(1988
                    and later) Digital rectal examination (DRE) Screening Code:
                    G0102. Procedure Codes for SEER-Medicare Analyses.
                    http://healthcaredelivery.cancer.gov/seermedicare/

Men Ever Received Biopsy[Age,Grade]=
                    Cx LocoRegional M0[Age,Grade]+Cx Distant M1[Age,Grade]+Sx LocoRegional M0[
Age,Grade]+Sx Distant M1[Age,Grade]+SUM(Nr Treated by age grade treatment[Age
,Grade,Treatment!])
Units: People
missing men coming from "biopsy+negative result" flow

Men Ever Received FP=
                    0
Units: People
different than current % of men with a FP

Metastasis=
                    0

Units: People/year

Metastasis Hazard Mx=
        1
Units: 1/year
Metastasis hazard for 1=low grade cases, 2=high grade cases, Low
                Grade=Gleason score 2-7, High Grade=Gleason Score 8-10.

Metastasis Hazard Mx1[Grade]=
        0.05,0.01,0

                {LATENT DISEASE DOESNT GET METASTASIZED!}
Units: 1/year
hazard of transition to metastatic disease:
                0.0004---0.0005,0.0003,0 0.05,0.01,0 0.0004:
                http://www.ncbi.nlm.nih.gov/pubmed/20530126 page 713. we assume
                stage durations are distributed independently according to
                exponential distribvutions -pcsim 16 disease progression rates
                are independent of patient age, race, and date of disease onset,
                similar to other studies- PCSIM 0.06,0.03,0 Metastasis hazard
                for men with canbcer. Underwood et al., 2012:
                http://www.ncbi.nlm.nih.gov/pubmed/22302420 b=0.006 MCRPR= Mayo
                Clinic Radical Prostatectomy Registry, for patients under
                treatment. e=0.069 for patients not diagnosed (Ghani et al.,
                Scardino et al). TIME TO DEVELOP M1 DISEASE, CAN BE SUBSCRIPTED
                BY AGE Yearly hazard of metastasis in different preclinical
                stages (wever et al, 2009) paper has 9 parameters based on
                clinical stage: T1, T2, T3, pathologic grade: G6, G7, G8, and
                Metastasis: M0 for locoregional and M1 for distant. T2 total is
                0.0637, T3 total is 0.1767 underwood:
                http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3711512/ 0.069

Metastasis Hazard Mx2=
        0.0004
Units: 1/year
Metastasis hazard for 1=low grade cases, 2=high grade cases.
                Underwood et al., 2012 b=0.006 MCRPR= Mayo Clinic Radical
                Prostatectomy Registry, for patients under treatment. e=0.069
                for patients not diagnosed (Ghani et al., Scardino et al).

Metastasis Switch=
        1
Units: dmnl

Metastasis2=
        0
Units: People/year

Mortality Decrease All Ages Time Series 1979to2014:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G64')
Units: dmnl

Mortality Decrease Switch=
        1
Units: dmnl
equals to 1 if we want to allow decreases in future mortality
                rates, 0 implies 1990 mortality rates throughout the simulation

Mortality Decrease Time Series 35to44:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G58')
Units: dmnl

Mortality Decrease Time Series 45to54:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G59')
Units: dmnl

Mortality Decrease Time Series 55to64:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G60')
Units: dmnl

Mortality Decrease Time Series 65to74:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G61')
Units: dmnl

Mortality Decrease Time Series 75plus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G69')
Units: dmnl

Mortality Decrease Time Series 75to84:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G62')
Units: dmnl

Mortality Decrease Time Series 85plus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'G63')
Units: dmnl

"Mu D+"=
        2
Units: dmnl
1.2 Old value=1.9. Mean value of the distribution of the test
                outcome for the diseased (D+) population. UNKNOWN, but there are
                some estimates. The mean (±SD) PSA value was 1.78±0.92 ng per
                milliliter among the 449 men with prostate cancer and 1.34±0.86
                ng per milliliter among the 2501 men without cancer (P<0.001).
                The annual increase in the PSA level during the seven years of
                the study, which was computed by means of linear regression
                (range, 0.32 to 0.46 ng per milliliter per year), was positively
                associated with the risk of prostate cancer (P<0.001).
                http://www.nejm.org/doi/full/10.1056/NEJMoa031918#t=article

"Mu D-"=
        1.2
Units: dmnl
1--old 0.6 Old value=1 or 0.9. Mean value of the distribution of
                the test outcome for the healthy (D-) population. UNKNOWN, there
                are some estimates, not sure how reliable. The mean (±SD) PSA
                value was 1.78±0.92 ng per milliliter among the 449 men with
                prostate cancer and 1.34±0.86 ng per milliliter among the 2501
                men without cancer (P<0.001). The annual increase in the PSA
                level during the seven years of the study, which was computed by
                means of linear regression (range, 0.32 to 0.46 ng per
                milliliter per year), was positively associated with the risk of
                prostate cancer (P<0.001).
                http://www.nejm.org/doi/full/10.1056/NEJMoa031918#t=article
                Carter et al., 1992- 0.84 µg/L± 0.063 µg/L, 7.5%; 2.9
                µg/L±0.12 µg/L, 4%; and 40 µg/L± 1.6 µg/L, 4%.

Multiplier for Hazard of Clinical Diagnosis=
        20
Units: dmnl
19.1334 http://www.ncbi.nlm.nih.gov/pubmed/20530126-- page 713.

Mx2[Grade,Treatment]=
        Metastasis Hazard Mx1[Grade]*relMxTxM0[Treatment]
Units: 1/year

mxCxM0[Age,Grade]=
        Cx LocoRegional M0[Age,Grade]*Metastasis Hazard Mx1[Grade]*Metastasis Switch
Units: People/year
Metastasis rate (mx) from local-regional (M0) disease to distant
           disease (M1)

mxM0[Age,Grade]=
        Ux LocoRegional M0[Age,Grade]*Metastasis Hazard Mx1[Grade]*Metastasis Switch
Units: People/year
Metastasis rate (mx) from local-regional (M0) disease to distant
           disease (M1)

mxSxM0[Age,Grade]=
        Sx LocoRegional M0[Age,Grade]*Metastasis Hazard Mx1[Grade]*Metastasis Switch
Units: People/year
Metastasis rate (mx) from local-regional (M0) disease to distant
           disease (M1)

mxTxCxM0[Age,Grade,Treatment]=
        Tx CxM0[Age,Grade,Treatment]*Mx2[Grade,Treatment]*Metastasis Switch
Units: People/year
Metastasis rate from local-regional (M0) disease to distant
           disease (M1)

mxTxSxM0[Age,Grade,Treatment]=
        Tx SxM0[Age,Grade,Treatment]*Mx2[Grade,Treatment]*Metastasis Switch
Units: People/year
Metastasis rate from local-regional (M0) disease to distant
           disease (M1)

"Neg Like Ratio (NLR)"=
        (1-"True Pos Rate (TPR)"[d1])/(1-"False Pos Rate (FPR)"[d1])
Units: dmnl
The ratio between the probability of a negative test result
           given the presence of the disease and the probability of a
           negative test result given the absence of the disease, i.e. =
           False negative rate / True negative rate = (1-Sensitivity) /
           Specificity

"Neg Pred Value (NPV)"=
        "True Neg Rate (TNR)"[d1]/("True Neg Rate (TNR)"[d1]+"False Neg Rate (FNR)"
[d1])
Units: dmnl
The probability that the disease is not present when the test is
           negative (expressed as a percentage). NPV= d / (b+d) =
           specs*(1-prevalence)/(1-sens)*prevalence+specs*(1-prevalence)

Net Change in Popn=
        Total Popn-SUM(Adult men popn millions initial 1980[Age!])
Units: People

Net International Migration Data:INTERPOLATE::=
        Net International Migration Series*1000
Units: People/year

Net International Migration Series:=
        GET XLS DATA('PSA.xlsx','NP2014-T15','4', 'B53')

Units: People/year

NetImRate Data=
        Adult net immigration rate series(Time)*ImmSwitch
Units: 1/year
OR JUST USE 0.003, OR JUST DELETE AND ADJUST MORTALITY
                RATE--JACK Adult net immigration rate series(Time)

NHANES biopsy compliance=
        1
Units: dmnl
http://wwwn.cdc.gov/nchs/nhanes/search/default.aspx 2003-2004:
                yes:25, no:20, cum:121 2005-2006: yes:15, no:7, cum: 52 these
                are men with high PSA result (PSA>4 NG/ML)

NHANES ever had PSA=
        1
Units: People
KIQ321: http://wwwn.cdc.gov/nchs/nhanes/search/default.aspx
                2002: 598 YES, 857 NO, CUMULATIVE 2386 MEN over 40--41% for men
                over 40 2004:

nominator=
        F2+F3+F4
Units: dmnl

Nr Men Ever Had PSA[Age]=
        At Risk and Screened FP[Age]+At Risk and Screened TN[Age]+SUM(Sx Distant M1
[Age,Grade!])+SUM(Sx LocoRegional M0[Age,Grade!])+SUM(Tx SxM0[Age,Grade!,Treatment
!])+SUM(Tx SxM1[Age,Grade!,Treatment!])+SUM(Tx SxM0M1[Age,Grade!,Treatment!
])
Units: People
current number of men who ever received a PSA test in their
                life, prevalence variable. At Risk and Screened FP[Age]+At Risk
                and Screened TN[Age]+SUM(Sx Distant M1[Age,Grade!])+SUM("Sx
                Loco-regional M0"[Age,Grade!])+SUM(Tx
                CxM0[Age,Grade!,Treatment!])+SUM(Tx
                CxM1[Age,Grade!,Treatment!])+SUM(Tx
                SxM0[Age,Grade!,Treatment!])+SUM(Tx
                SxM1[Age,Grade!,Treatment!])+SUM("TxCxM0-M1"[Age,Grade!,Treatment
                !])+SUM("TxSxM0-M1"[Age,Grade!,Treatment!])

Nr Men Ever Had PSA over 50=
        SUM(Nr Men Ever Had PSA[Age50Plus!])
Units: People

Nr of FPs Per Person=
        1.5
Units: FP/person

nr of years=
        1
Units: year

Nr Treated by age[Age]=
        SUM(Nr Treated by age grade[Age,Grade!])
Units: People
1.38e+007 in 2010. Assuming constant incidence, survival, and
                cost, projection is 13.8 and 18.1 million cancer survivors in
                2010 and 2020, respectively, with associated costs of cancer
                care of 124.57 and 157.77 billion 2010 US dollars.

http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
survivor: any person diagnosed with cancer, from the time of
initial diagnosis until his or her death.
http://costprojections.cancer.gov/cancer.prevalance.html

Nr Treated by age grade[Age,Grade]=
        SUM(Nr Treated by age grade treatment[Age,Grade,Treatment!])
Units: People
SUM(Nr Treated by age grade
        treatment[Age,Grade,Treatment!])+Total Diagnosed by age
        grade[Age,Grade] Cancer survivor: any person diagnosed with
        cancer, from the time of initial diagnosis until his or her
        death. Assuming constant incidence, survival, and cost,
        projection is 13.8 and 18.1 million cancer survivors in 2010 and
        2020, respectively, with associated costs of cancer care of
        124.57 and 157.77 billion 2010 US dollars.
        http://jnci.oxfordjournals.org/content/103/2/117.long.
        http://costprojections.cancer.gov/cancer.prevalance.html

Nr Treated by age grade treatment[Age,Grade,Treatment]=
        Tx CxM0[Age,Grade,Treatment]+Tx CxM0M1[Age,Grade,Treatment]+Tx SxM0[Age,Grade
,Treatment]+Tx SxM0M1[Age,Grade,Treatment
        ]+Tx SxM1[Age,Grade,Treatment]+Tx CxM1[Age,Grade,Treatment]
Units: People
Cancer survivor: any person diagnosed with cancer, from the time
        of initial diagnosis until his or her death. Assuming constant
        incidence, survival, and cost, projection is 13.8 and 18.1
        million cancer survivors in 2010 and 2020, respectively, with
        associated costs of cancer care of 124.57 and 157.77 billion
        2010 US dollars.
        http://jnci.oxfordjournals.org/content/103/2/117.long.
        http://costprojections.cancer.gov/cancer.prevalance.html

Nr Treated by grade[Grade]=
        SUM(Nr Treated by age grade[Age!,Grade])
Units: People

Nr Treated by grade treatment[Grade,Treatment]=
        SUM(Nr Treated by age grade treatment[Age!,Grade,Treatment])
Units: People
Cancer survivor: any person diagnosed with cancer, from the time
        of initial diagnosis until his or her death. Assuming constant
        incidence, survival, and cost, projection is 13.8 and 18.1
        million cancer survivors in 2010 and 2020, respectively, with
        associated costs of cancer care of 124.57 and 157.77 billion
        2010 US dollars.
        http://jnci.oxfordjournals.org/content/103/2/117.long.
        http://costprojections.cancer.gov/cancer.prevalance.html

Nr Treated by treatment[Treatment]=
        SUM(Nr Treated by grade treatment[Grade!,Treatment])
Units: People
Cancer survivor: any person diagnosed with cancer, from the time
        of initial diagnosis until his or her death. Assuming constant
        incidence, survival, and cost, projection is 13.8 and 18.1
        million cancer survivors in 2010 and 2020, respectively, with
        associated costs of cancer care of 124.57 and 157.77 billion
        2010 US dollars.
        http://jnci.oxfordjournals.org/content/103/2/117.long.
        http://costprojections.cancer.gov/cancer.prevalance.html

Number of Adverse Events AE=
        1
Units: dmnl

Number of Biopsies Per Dplus Case=
        1
Units: Biopsies/person

Number of Biopsies Per FP Case=
        1.75
Units: Biopsies/person
Wilt et al., 2014--For 1000 men undergoing screening every 1 to
                4 years and followed for up to 14 years, approximately 1 in 4
                will have an elevated PSA test (80% are false positive), and
                most will undergo at least one set of prostate biopsies, often
                more than one. Among men undergoing a biopsy, one-third or more
                will incur at least moderate harm such as pain, bleeding, and
                infection. Between one and seven in 100 will be hospitalized
                within 30 days, typically for sepsis, many with
                antibiotic-resistant organisms (1,2).--
                http://www.uptodate.com/contents/screening-for-prostate-cancer
                People with FP continue having biopsies regularly unless they
                get a diagnosis of BPH or something else. --see email for an
                extreme case with 63 biopsies, with high PSA, no cancer or BPH

Number of Cancer Survivors=
        1.38e+007
Units: People
in 2010. Assuming constant incidence, survival, and cost, we
                projected 13.8 and 18.1 million cancer survivors in 2010 and
                2020, respectively, with associated costs of cancer care of
                124.57 and 157.77 billion 2010 US dollars.
                http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
                survivor: any person diagnosed with cancer, from the time of
                initial diagnosis until his or her
                death.http://costprojections.cancer.gov/cancer.prevalance.html

Number of Medicare Claims=
        1
Units: dmnl
http://healthcaredelivery.cancer.gov/seermedicare/aboutdata/hcpcs
                .html Number of claims increased from 164.000 in 1991 to 286.532
                in 2013. but data is a conservative estimate and doesnt include
                comminity outreach etc, real numbers are higher.

Number of Patients with Prescription Drugs in DME file by NDC Brand Name=
        1
Units: People
http://healthcaredelivery.cancer.gov/seermedicare/aboutdata/ndc_f
                requency.html increased from 17 in 1994 to 531 in 2012, then
                decreased to 432 in 2013.

Number of Prostate Cancer Patients with Jcode HCPCS in DME by claim year=
        1
Units: People
increased from 26.483 in 1994 to 92.924 in 2010, then decreased
                to 82.269 by 2013.
                http://healthcaredelivery.cancer.gov/seermedicare/aboutdata/ndc_f
                requency.html

Number of Tests Per Person=

1
Units: tests/person

ocDeathsSwitch=
1
Units: dmnl

"oldTable for Effect of Age on D+"(
[(30,0)-(90,0.09)],(30,0.008),(35,0.008),(40,0.01),(45,0.015),(50,0.02),(55
,0.026),(60,0.034),(65,0.046),(70,0.059),(75,0.07),(80,0.075),(85,0.078),(90
,0.079),(90,0.079))
Units: dmnl
http://www.nature.com/nrg/journal/v5/n10/fig_tab/nrg1450_F2.html
lifetime risk of breast cancer carriers vs non-carriers
http://pubsonline.informs.org/doi/citedby/10.1287/opre.1110.1019-
-Table 4 Breast cancer risk as a function of personal history of
screening--Alagoz and Ayer, 2012

One Time Treatment Cost=
Base One Time Treatment Cost*Table Eff of T on Cost of Treatment(Technology T
)
Units: $/person

Onset=
0
Units: People/year

Onset Hazard Ox=
1
Units: 1/year
Onset hazard for PCa.

Optimal=
1
Units: dmnl

Optimal HBR=
1
Units: dmnl
Optimal Harms to Benefits Ratio (HBR)==1

Optimal ROC=
IF THEN ELSE(Time>0, 1 , 0)
Units: dmnl

Overall Current Screen Fraction=
SUM(Current Screened Fraction[Age!]*Total Popn by age[Age!])/SUM(Total Popn by age
[Age!])
Units: dmnl
the fraction of people who would screen today, NOT AGE ADJUSTED

Overdiagnosed Fraction of dxPCa=
ZIDZ(dxRateSxIndolent,(sxRateTotal+cxRateTotal))
Units: dmnl
overdiagnosis fraction for all (screen and clinically detected)
cancers (pure overdiagnosis of an indolent cancer, otherwise not
progressive)

Overdiagnosed Fraction of dxPCa after XX=
ZIDZ((dxRateSxIndolent+XXocSxPCa+XXoxCxPCa),(dxRateTotal+XXocSxPCa+XXoxCxPCa
))

Units: dmnl

Overdiagnosed Fraction of sxPCa=
        ZIDZ(dxRateSxIndolent,sxRateTotal)
Units: dmnl
overdiagnosis fraction for all screen detected cancers (pure
                overdiagnosis of an indolent cancer, otherwise not progressive)

Overdiagnosed Fraction of sxPCa after XX=
        ZIDZ((dxRateSxIndolent+XXocSxPCa),(sxRateTotal+XXocSxPCa))
Units: dmnl

Overdiagnosis Definition=
        1
Units: dmnl
Provides measures of the event (which typically cannot be
                observed) where screening detects cancer that would have
                otherwise gone undetected with lifetime follow up. That is,
                would not have surfaced in the person's lifetime.
                https://resources.cisnet.cancer.gov/registry/glossary/#outputsout
                comesscreeningoverdiagnoses OR: overdiagnosis as the proportion
                of patients whose cancer was detected through PSA screening but
                who did not SURVIVE LONG ENOUGH to have their cancer clinically
                diagnosed (Yao and Yao, 2002). This definition is distinctly
                different from that most often cited in textbooks and in the
                literature where overdiagnosis is usually defined as the
                identification of disease that would not have produced signs or
                symptoms before death (10,11). These two definitions of
                overdiagnosis would be the same only if all clinically diagnosed
                cancers produced signs and/or symptoms. In fact, we know that
                this situation probably is not the case, perhaps because most
                (-70%) prostate cancers reside in the peripheral zone of the
                prostate rather than next to the urethra (or other common
                symptom-producing structures) in the transition zone (12).
                Because asymptomatic, localized, or even regional disease (i.e.,
                incident disease) can precede symptomatic disease (12,16,17) by
                many years [the time from clinical diagnosis to just progressive
                disease can exceed 10 years in certain cohorts (18)], many more
                men will die of causes other than prostate cancer during the
                time interval from clinical diagnosis to the development of
                signs and/or symptoms. That is, the additional period of time
                required to experience symptomatic disease allows patients to
                die of alternative causes and thus be overdiagnosed. Hence, the
                use of incident, rather than symptomatic, disease by Etzioni et
                al. effectively decreases the opportunity to die of a competing
                cause, thereby decreasing the likelihood of overdiagnosis (Fig.
                1). As the authors point out, the use of a mortality end point
                was the approach used by McGregor et al. (25), who found that
                84% of screen-detected cancers would be overdiagnosed.

P tumor grade at onset POx[Grade]=
        Init Grade[Grade]
Units: dmnl
Fraction of (Onset) for 1- High grade, 2- Low grade, 3- Indolent
                disease. Sensitivity for indolent fraction: 0.2-0.6, see how
                overdiagnosis rates change, try to approximate indolent
                fraction, based on age-specific prevalence. 80% of disease is of
                non-progressive type. Greater than 80% of men with newly
                diagnosed cancers have local or regional stage disease (Ries et
                al., Nat. Cancer Inst. 2002)

P tumor low grade at onset pOx1=
        1
Units: dmnl
Probability a tumor is low grade at onset

"P(T-/D+)"=
        0.15
Units: dmnl
should be endogenous. changes by actual biopsy threshold, and
                if underlying PSA distributions change (second one outside of
                model scope). 15% of patients with a test result less than 4
                ng/ml have prostate cancer. among these, 15% have metastatic
                prostate cancer. add ref here.

PCa Deaths as a Fraction of Total Deaths=
        ZIDZ(XXpcTotal,(XXpcTotal+XXocTotal))
Units: dmnl
around 3% per year, out of 100%

PCa Deaths Per 100000 Data:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'B4')
Units: 1/year
Number of New Cases and Deaths per 100,000: The number of new
                cases of prostate cancer was 147.8 per 100,000 men per year. The
                number of deaths was 22.3 per 100,000 men per year. These rates
                are age-adjusted and based on 2007-2011 cases and deaths.

PCa Deaths Per 100thou=
        XXpcTotal/Total Popn*100000
Units: 1/year

PCa Incidence Over 35(
        [(1999,0)-(2012,200)],(1999,169.7),(2000,172),(2001,174),(2002,171.9),(2003
,156.7),(2004,152.4),(2005,149.8),(2006,159.3),(2007,163.6),(2008,150.6),(2009
,142.2),(2010,132.6),(2011,131.2),(2012,105.3))
Units: 1/year
https://nccd.cdc.gov/uscs/cancersbyraceandethnicity.aspx per
                100.000 men, age adjusted. AGE>35 per 100.000 men

PCa Incidence Over 50(
        [(2000,0)-(2020,600)],(2005,534.9),(2008,540.8),(2010,505),(2012,416.2))
Units: 1/year
Jemal et al., 2015:
                http://jama.jamanetwork.com/article.aspx?articleid=2470446 per
                100.000 men

PCa Incidence Per 100000 Data:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'B3')
Units: 1/year
Number of New Cases and Deaths per 100,000: The number of new
                cases of prostate cancer was 147.8 per 100,000 men per year. The
                number of deaths was 22.3 per 100,000 men per year. These rates
                are age-adjusted and based on 2007-2011 cases and deaths.

PCa Mortality Data=
        1
Units: 1/year
Mortality data is given in stage and grade.
                http://knowyourchances.cancer.gov/custom_charts.php

PCa Prevalence Data:=

GET XLS DATA('PSA.xlsx','Sheet1','2', 'G9')
Units: People
Prevalence of this cancer: In 2011, there were an estimated
                    2,707,821 men living with prostate cancer in the United States.
                    2.311.000 in 2010; 2,707,821 in 2011. 3.265.000 projected in
                    2020, a 34% increase. Mariotto et al., 2010. Cancer survivor:
                    any person diagnosed with cancer, from the time of initial
                    diagnosis until his or her death.
                    https://costprojections.cancer.gov/graph.php#

PCa Prevalence Data3=
        2.311e+006
Units: dmnl
2.311.000 in 2010. 3.265.000 projected in 2020, a 34% increase.
                    Mariotto et al., 2010.

PCaXXSwitch=
        1
Units: dmnl

pChgTxM0[ActiveSurveillance,TreatmentTo]=
        0,0,0
pChgTxM0[RadioTheraphy,TreatmentTo]=
                0,0,0
pChgTxM0[RadicalProstatectomy,TreatmentTo]=
                0,0,0
        Units: 1/year
        john's suggestion 0,0.4,0.1 0.1,0,0.1

pChgTxM1[ActiveSurveillance,TreatmentTo]=
        0,0,0
pChgTxM1[RadioTheraphy,TreatmentTo]=
                0,0,0
pChgTxM1[RadicalProstatectomy,TreatmentTo]=
                0,0,0
        Units: 1/year
        john's suggestion 0,0.3,0.5 0,0,0.5

PDF of T=
        "PDF of Threshold for D+"*"% D+"+"PDF of Threshold for D-"*(1-"% D+")
Units: dmnl

"PDF of Threshold for D+"=
        1/(Cutoff X*"Sigma D+"*(2*PI)^0.5)*EXP((-1)*((LnX-"Mu D+")^2)/(2*"Sigma D+"
^2))
Units: dmnl
Probability density function of Threshold T for diseased (D+)
                    population---LOGNORMAL PDF of PSA distribution for D+
                    population. 1/("Stdev D+"*(2*PI)^0.5)*exp((-1)*((Cutoff X-"Mean
                    D+")^2)/(2*"Stdev D+"^2)) for NORMAL

"PDF of Threshold for D-"=
        1/(Cutoff X*"Sigma D-"*(2*PI)^0.5)*EXP((-1)*((LnX-"Mu D-")^2)/(2*"Sigma D-"
^2))
Units: dmnl
Probability density function of Threshold T for healthy (D-)
                    population--LOGNORMAL. PDF of PSA distribution for D-
                    population. 1/("Stdev D-"*(2*PI)^0.5)*exp((-1)*((Cutoff_X-"Mean
                    D-")^2)/(2*"Stdev D-"^2)) for NORMAL

PDminus=

1-PDplus
Units: dmnl
layperson purely assuming D- as being equal to T-

PDplus=
    ZIDZ(TplusAll,Total F)
Units: dmnl
layperson purely assuming D+ as being equal to T+

People with Unnecessary Biopsies Per Year[Age]=
    First Time FP Rate Per Year[Age]*BiopCompM0
Units: People/year

per100000men=
    100000
Units: People

Perceived HBR T[group]=
    SMOOTH3(IF THEN ELSE(Time<Guideline Start Year[group],1+InitialHBRBias[group
],HBR For Action[group]),HBR Trans Delay)
Units: dmnl
"Perceived" Harms to Benefits Ratio (HBR) is the exponentially
        smoothed value of the "actual" HBR

Percent of Pop Diagnosed=
    15
Units: dmnl
increases from 8 to 15

Percent of seniors of males over 35:INTERPOLATE::=
    GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B62')
Units: People
percent of 35 plus

Percent Over 65=
    Total Popn above 65/Total Popn*100
Units: dmnl

Percent Over 65 DATA:=
    GET XLS DATA('PSA.xlsx','NP2014-T9','4', 'B62')
Units: dmnl
65+% OR 35+ POPULATION

Percentage of Men with PSA test last year(
    [(2000,0)-(2020,50)],(2005,36.9),(2008,40.6),(2010,37.8),(2013,30.8))
Units: dmnl
jemal et al., 2015--men over 50, who had psa test in the last 12
        months

Percentages in Each Stage=
    1
Units: dmnl
Stages 0-I-II is localized disease. In 1997, stage A comprises
        44%, B 46%, C 4% and D 6%. source?? 1992: 5.4; 22.8; 41.1; 18;
        12.6 1995: 2.0; 24.9; 49.7; 13.0; 10.3-- from Mettlin et al.,
        1998--stages 0-IV, from NCDB.

Percentages Receiving Treatment of Interest=
    1 {GET DATA: http://oliver.facs.org/BMPub/index.cfm by diagnosis year, first course treatment}
Units: dmnl
Treatment patterns should be described by clinical stage

(Meltzer et al., 2002, AJPH). We categorized treatment as surgery (RP), radiation including brachtherapy (RT), or neither treatment, expectant management (EM). Surgery combined with radiation is categorized as RP. In 1997, 31% of patients receive RP, 32% receive RT, 37% receive neither (Meltzer et al., 2001).

PI=
        3.14159
Units: dmnl
PI = 3.14159

PofTminusDminus=
        Specificity
Units: dmnl
p(t-/d-)=p(d-/t-)*p(t-)/ p(d-) = specs *p(t-)/ p(d-)

Pop Eligible for HRT=
        Affected Population*Technology T
Units: People

Pop Increase2[Age]=
        Male Pop Turning 35[Age]+Adult Net Immigration by Age[Age]
Units: People/year

Pop Time Series 1980to2014[AgeGroup35to44]:=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F41')
Pop Time Series 1980to2014[AgeGroup45to54]:=
                GET XLS DATA('PSA.xlsx','Sheet1','2', 'F42')
Pop Time Series 1980to2014[AgeGroup55to64]:=
                GET XLS DATA('PSA.xlsx','Sheet1','2', 'F43')
Pop Time Series 1980to2014[AgeGroup65to74]:=
                GET XLS DATA('PSA.xlsx','Sheet1','2', 'F44')
Pop Time Series 1980to2014[AgeGroup75plus]:INTERPOLATE::=
                GET XLS DATA('PSA.xlsx','Sheet1','2', 'F67')
        Units: People

Pop Time Series 35to44:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F41')
Units: People
http://wonder.cdc.gov/mortSQL.html

Pop Time Series 45to54:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F42')
Units: People
http://wonder.cdc.gov/mortSQL.html

Pop Time Series 55to64:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F43')
Units: People

Pop Time Series 65to74:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F44')
Units: People
http://wonder.cdc.gov/mortSQL.html

Pop Time Series 75plus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F67')
Units: People
http://wonder.cdc.gov/mortSQL.html

Pop Time Series 75to84:INTERPOLATE::=

GET XLS DATA('PSA.xlsx','Sheet1','2', 'F45')
Units: People
http://wonder.cdc.gov/mortSQL.html

Pop Time Series 85plus:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F46')
Units: People

Popn 35to39=
        SUM(Total Popn by age[Age35to39!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
                localized stage before the age of 65 years is associated with a
                specific survival of less than 30%.
                http://www.ncbi.nlm.nih.gov/pubmed/9410329

Popn 35to44=
        SUM(Total Popn by age[AgeGroup35to44!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
                localized stage before the age of 65 years is associated with a
                specific survival of less than 30%.
                http://www.ncbi.nlm.nih.gov/pubmed/9410329

Popn 40to49=
        SUM(Total Popn by age[AgeGroup40to49!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
                localized stage before the age of 65 years is associated with a
                specific survival of less than 30%.
                http://www.ncbi.nlm.nih.gov/pubmed/9410329

Popn 45to54=
        SUM(Total Popn by age[AgeGroup45to54!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
                localized stage before the age of 65 years is associated with a
                specific survival of less than 30%.
                http://www.ncbi.nlm.nih.gov/pubmed/9410329

Popn 50to59=
        SUM(Total Popn by age[AgeGroup50to59!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
                localized stage before the age of 65 years is associated with a
                specific survival of less than 30%.
                http://www.ncbi.nlm.nih.gov/pubmed/9410329

Popn 55to64=
        SUM(Total Popn by age[AgeGroup55to64!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
                localized stage before the age of 65 years is associated with a
                specific survival of less than 30%.
                http://www.ncbi.nlm.nih.gov/pubmed/9410329

Popn 60to69=
        SUM(Total Popn by age[AgeGroup60to69!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
                localized stage before the age of 65 years is associated with a

specific survival of less than 30%.
http://www.ncbi.nlm.nih.gov/pubmed/9410329

Popn 65to74=
       SUM(Total Popn by age[AgeGroup65to74!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
              localized stage before the age of 65 years is associated with a
              specific survival of less than 30%.
              http://www.ncbi.nlm.nih.gov/pubmed/9410329

Popn 70to79=
       SUM(Total Popn by age[AgeGroup70to79!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
              localized stage before the age of 65 years is associated with a
              specific survival of less than 30%.
              http://www.ncbi.nlm.nih.gov/pubmed/9410329

Popn 75plus=
       SUM(Total Popn by age[AgeGroup75plus!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
              localized stage before the age of 65 years is associated with a
              specific survival of less than 30%.
              http://www.ncbi.nlm.nih.gov/pubmed/9410329

Popn 80plus=
       SUM(Total Popn by age[Age80Plus!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
              localized stage before the age of 65 years is associated with a
              specific survival of less than 30%.
              http://www.ncbi.nlm.nih.gov/pubmed/9410329

Popn Below 35DATA:=
       GET XLS DATA('PSA.xlsx','Sheet1','2', 'F121')
Units: People

Popn death rate US 1990[AgeGroup35to39]=
       0.00281

       {change values with life tables data}
Popn death rate US 1990[AgeGroup40to44]=
              0.00339
Popn death rate US 1990[AgeGroup45to49]=
              0.00487
Popn death rate US 1990[AgeGroup50to54]=
              0.00747
Popn death rate US 1990[AgeGroup55to59]=
              0.01193
Popn death rate US 1990[AgeGroup60to64]=
              0.01882
Popn death rate US 1990[AgeGroup65to69]=
              0.0282
Popn death rate US 1990[AgeGroup70to74]=
              0.04288
Popn death rate US 1990[AgeGroup75to79]=
              0.06578
Popn death rate US 1990[AgeGroup80plus]=
              0.14

{0.108257 for 80-84, 0.185761 for 85+}
Units: 1/year
Popn death rate. Based on sex-age-specific Census and Vital
    Stats. Use Vital Stats deaths (M, Agegp) by Census popn (M,
    Agegp) to calculate agegp-specific death rates for 2000. Divide
    by the appropriate time series for decrease in mortality from
    1990 to 2000 (M 30-64, M65+), to get the adjusted death rate
    initial values for 1990. 0.002,0.0065,0.057 in PRISM for ages
    18-29,30-65, and 65+ Arias E (2006) United states life tables.
    Natl Vital Stat Rep58(21):1-40 Etzioni et al., 1999- Table 1.
    Age specific mortality rates, % all cause-mortality:
    http://www.ncbi.nlm.nih.gov/pubmed/10458357 Underwood et al
    2012- Table 3: http://www.ncbi.nlm.nih.gov/pubmed/22302420 Cowen
    et al. 1993-Table 1: annual mortality rate, excluding PCa--
    given for blacks and whites

Popn death rate US 1990 0[Age]=
   0.002488,0.002956,0.00452,0.007463,0.012215,0.019398,0.029087,0.046021,0.069881
,0.14
Units: 1/year
Popn death rate. Based on sex-age-specific Census and Vital
    Stats. Use Vital Stats deaths (M, Agegp) by Census popn (M,
    Agegp) to calculate agegp-specific death rates for 2000. Divide
    by the appropriate time series for decrease in mortality from
    1990 to 2000 (M 30-64, M65+), to get the adjusted death rate
    initial values for 1990. 0.002,0.0065,0.057 in PRISM for ages
    18-29,30-65, and 65+ Arias E (2006) United states life tables.
    Natl Vital Stat Rep58(21):1-40 Etzioni et al., 1999- Table 1.
    Age specific mortality rates:
    http://www.ncbi.nlm.nih.gov/pubmed/10458357 Underwood et al
    2012- Table 3: http://www.ncbi.nlm.nih.gov/pubmed/22302420 Cowen
    et al. 1993-Table 1: annual mortality rate, excluding PCa--
    given for blacks and whites

Popn death rate US 1990v2[AgeUnder65]=
   0.0065
Popn death rate US 1990v2[Age65Plus]=
    0.057
  Units: 1/year
  Popn death rate. Based on sex-age-specific Census and Vital
    Stats. 0.002,0.0065,0.057 in PRISM for ages 18-29,30-65, and 65+
    Arias E (2006) United states life tables. Natl Vital Stat
    Rep58(21):1-40 Etzioni et al., 1999- Table 1. Age specific
    mortality rates: http://www.ncbi.nlm.nih.gov/pubmed/10458357
    Underwood et al 2012- Table 3:
    http://www.ncbi.nlm.nih.gov/pubmed/22302420 Cowen et al.
    1993-Table 1: annual mortality rate, excluding PCa-- given for
    blacks and whites

Popn millions turning 35 time series Data:INTERPOLATE::=
   GET XLS DATA('PSA.xlsx','Sheet1','2', 'G73')
Units: People/year
Census: Statistical Abstract of the United States 2012, Table 7;
    "resident population by sex and age: 1980 to 2010". 5.1573e+007
    for men under 65, 1.2495e+007 for men above 65

"Pos Like Ratio (PLR)"=
   "True Pos Rate (TPR)"[d1]/"False Pos Rate (FPR)"[d1]
Units: dmnl
The ratio between the probability of a positive test result

given the presence of the disease and the probability of a
positive test result given the absence of the disease, i.e. =
True positive rate / False positive rate = Sensitivity /
(1-Specificity)

"Pos Pred Value (PPV)"=
"True Pos Rate (TPR)"[d1]/("True Pos Rate (TPR)"[d1]+"False Pos Rate (FPR)"
[d1])
Units: dmnl
The probability that the disease is present when the test is
positive (expressed as a percentage). PPV = a / (a+c) =
sens*prevalence/sens*prevalence+(1-specificity)*(1-prevalence)

"Post-Metastasis Clinical Diagnosis Hazard MCx11"=
1
Units: 1/year
Post metastasis clinical diagnosis hazard (1= for low-grade
cases, 2=for high-grade cases). Low Grade=Gleason score 2-7,
High Grade=Gleason Score 8-10.

Postmetastasis Clinical Diagnosis Hazard MCx[Grade]=
Premetastasis Clinical Diagnosis Hazard Cx[Grade]*Multiplier for Hazard of Clinical Diagnosis
Units: 1/year
Post metastasis clinical diagnosis hazard (0= for low-grade
cases, 1=for high-grade cases). Low Grade=Gleason score 2-7,
High Grade=Gleason Score 8-10. use a time constabt of 6 months
or so

Postmetastasis Clinical Diagnosis Hazard MCx2=
Premetastasis Clinical Diagnosis Hazard Cx2*Multiplier for Hazard of Clinical Diagnosis
Units: 1/year
Post metastasis clinical diagnosis hazard (1= for low-grade
cases, 2=for high-grade cases) Low Grade=Gleason score 2-7, High
Grade=Gleason Score 8-10.

pp=
0
Units: People/year

pp2=
0
Units: People/year

PrCancerDeathWithoutScreen=
0.1
Units: dmnl
endogeneous?

PrCancerDeathWithScreen=
0.01
Units: dmnl
endogeneous?

"Pre-Metastasis Clinical Diagnosis Hazard Cx11"=
1
Units: 1/year
Pre-metastasis clinical diagnosis hazard (`1=for low grade
cases, 2=for high grade cases). Low Grade=Gleason score 2-7,
High Grade=Gleason Score 8-10.

Premetastasis Clinical Diagnosis Hazard Cx[Grade]=

273

0.03,0.02,0
Units: 1/year
0.01,0.005,0 0.0015-http://www.ncbi.nlm.nih.gov/pubmed/20530126
Pre-metastasis clinical diagnosis hazard, by grade, also
increases by calendar year (1=for high grade cases, Gleason
score 8-10, 2=low grade cases, Gleason score 2-7, 3= indolent
cases, any Gleason). Clinical diagnosis hazard is 0 for latent
disease, has no symptoms throughout life, by definition --The
probability of clinical diagnosis by age 85 in the absence of
other-cause death ranges from 13% for the 1895-1900 cohort to
20% for the 1940-1945 cohort. Etzioni et al., 2008 med dec
making. 0.01,0.005,0 0.002,0.001,0

Premetastasis Clinical Diagnosis Hazard Cx OLD[AgeGroup35to44]=
0
Premetastasis Clinical Diagnosis Hazard Cx OLD[AgeGroup45to54]=
0.0015
Premetastasis Clinical Diagnosis Hazard Cx OLD[AgeGroup55to64]=
0.01
Premetastasis Clinical Diagnosis Hazard Cx OLD[AgeGroup65to74]=
0.025
Premetastasis Clinical Diagnosis Hazard Cx OLD[AgeGroup75plus]=
0.04
Units: 1/year
Pre-metastasis clinical diagnosis hazard, by grade, also
increases by calendar year (1=for high grade cases, Gleason
score 8-10, 2=low grade cases, Gleason score 2-7, 3= indolent
cases, any Gleason). Clinical diagnosis hazard is 0 for latent
disease, has no symptoms throughout life, by definition --The
probability of clinical diagnosis by age 85 in the absence of
other-cause death ranges from 13% for the 1895-1900 cohort to
20% for the 1940-1945 cohort. Etzioni et al., 2008 med dec
making. 0.002,0.001? 0.01,0.005,0

Premetastasis Clinical Diagnosis Hazard Cx2=
0.0015
Units: 1/year
Pre-metastasis clinical diagnosis hazard (`1=for low grade
cases, 2=for high grade cases) Low Grade=Gleason score 2-7, High
Grade=Gleason Score 8-10.

Present Time=
IF THEN ELSE(Time=2013 , 200 , 0)
Units: year

Probability of Disease[Dplus]=
"Age Specific Prevalence D+"*(1-Fract Indolent of Dplus)
Probability of Disease[Dminus]=
1-"Age Specific Prevalence D+"
Probability of Disease[Dzero]=
"Age Specific Prevalence D+"*Fract Indolent of Dplus
Units: dmnl
Prevalance of cancer in the target population. Data for D+
doesnt exist, and usually the data that comes from autopsy
series is used to this purpose.

Probability of Test Outcome[testoutcome,diseasestate]=
Probability of Test Outcome Conditioned on Disease State[testoutcome,diseasestate
]*Probability of Disease[diseasestate]
Units: dmnl
Probability of the test outcome

274

Probability of Test Outcome Conditioned on Disease State[Tplus,Dplus]=
    Sensitivity
Probability of Test Outcome Conditioned on Disease State[Tplus,Dminus]=
        1-Specificity
Probability of Test Outcome Conditioned on Disease State[Tminus,Dplus]=
        1-Sensitivity
Probability of Test Outcome Conditioned on Disease State[Tminus,Dminus]=
        Specificity
Probability of Test Outcome Conditioned on Disease State[Tplus,Dzero]=
        Sensitivity
Probability of Test Outcome Conditioned on Disease State[Tminus,Dzero]=
        1-Sensitivity
    Units: dmnl
    Probability of the test outcome conditioned on disease state
            adds up to 3

Progression rate of undiagnosed disease=
    1/12
Units: 1/year
The duration of the preclinical stage in the absence of
        screening (a random variable) is termed sojourn time.13.5 other
        estimate= 15

Projected Crude Death Fraction Data:=
    GET XLS DATA('PSA.xlsx','NP2014-T17','3', 'B17')
Units: 1/year

Projected Life Expectancy At Birth Data:=
    GET XLS DATA('PSA.xlsx','NP2014-T17','3', 'B16')
Units: year

Proportion of African Americans=
    2
Units: dmnl
has increased from 8.8% in 1992 to 11.8% in 1995, has
        implications on underlying disease incidence--Mettlin et al.,
        1998

PSA Screening Rate=
    SUM(PSA Screening Rate by age[Age!])
Units: tests/year

PSA Screening Rate by age[Age]=
    Screening Rate wo Disease[Age]+SUM(Screening Rate of Ux[Age,Grade!])+SUM(Screening Rate of Tx
[Age,Treatment
    !])+Screening Rate of Dx[Age]
Units: tests/year
total number of tests for all men with and without disease,
        during the simulation time horizon. The role of PSA testing
        patterns in the recent PCa incidence decline in the US (Legre et
        al., 1998)
        (1988,530),(1989,1776),(1990,3433),(1991,8186),(1992,12000),(1993
        ,12022) PEOPLE PER YEAR, OR PEOPLE PER 100.000?

Pseudo HBR[prof]=
    1-Weighted Disutility EB*Sensitivity of HBR to Utility
Pseudo HBR[advoc]=
        1-Weighted Disutility layperson*Sensitivity of HBR to Utility
    Units: dmnl

pTxM0[Treatment]=
       0.1,0.5,0.4
Units: dmnl
what if it doesnt add up to 1? Probability to choose particular
              treatment initially, when detected at M0 stage(1=Active
              Surveillance, AS 2=Radiotheraphy, RT 3=Radical Prostatectomy,
              RP) look at data at pop sector. treatment types for M0, is it
              also based on grade? i.e. subscript by grade? endogeneous?
              TREATMENT TRENDS CHANGED over time. ASK JOHN-HAZHIR. SUBSCRIPT
              BY AGE GROUP- old vs young have different treatments. the
              majority of men with clinically localized cancer are offered
              aggressive treatment with radical prostatectomy (RP) or
              radiation therapy (RT) (Fowler and Collins et al., JAMA,2000).
              The use of RP has increased substantially during 1990's (Lu-Yao
              and Friedman et al., 1997, Mettlin, 1997) from (Hoffman et al.,
              2003).

pTxM1[Treatment]=
       0.1,0.5,0.5
Units: dmnl
percent to choose particular treatment (1=Radical Prostatectomy,
              RP 2=Radiotheraphy) when detected at M1 stage these ratios
              differ for younger vs older men.

Public Perception Delay=
       2
Units: year
Patients perspective---The average time required to perceive/
              and comply with the recommendations for routine screening.
              1-Scientific data accumulation, translation and 2-Public
              perception delays are the major delays in evidence based
              guideline creation.

Public Weighing on R=
       0.4
Units: dmnl
Weight put on evidence base for the starting age of routine
              screening (as opposed to advocated starting age)

QALY Disutilities=
       0.05
Units: dmnl
Martin et al., 2013. the effect of Prostate cancer (and its
              treatment) on QOL was equivalent to a decrement of 0.05 in
              utility averaged over the entire survival period, with a
              plausible range of 0.00 to 0.10. The net effectiveness of each
              strategy (PSA screening versus no PSA screening) was quantified
              in terms of quality-adjusted life-years (QALYs). The average
              QALYs were calculated by weighting the time spent in each health
              state by the health-related QOL value (utility) associated with
              that state, where 0 = death and 1 = full health.
              https://www.mja.com.au/journal/2013/198/10/risk-assessment-guide-
              prostate-cancer-screening-decisions-cost-effectiveness

R and D=
       Fraction of HR Industry Revenue Allocated to RD*HR Revenue*Table Function for RandD
(Marginal Return to RD)
Units: $/year

R Switching[group]=
       IF THEN ELSE(Time>Guideline Start Year[group],Switch R[group], 0)

Units: dmnl
1986 is the year PSA screening has started.

Rate of Leaving Adult Age Category=
        Rate of Leaving Adult Age Category Series(Time)
Units: dmnl
unit?

Rate of Leaving Adult Age Category Series(
        [(1980,0)-(2040,2)],(1980,1),(1990,1.05),(2000,1.1),(2010,1),(2020,0.95),(
2030,0.9),(2040,1))
Units: dmnl
[(1980,0)-(2040,2)],(1980,1),(1990,1.05),(2000,1.1),(2010,1),(202
                0,0.95),(2030,0.9),(2040,1)
                [(1980,0)-(2040,2)],(1980,1),(1990,1.05),(2000,1.05),(2010,0.95),
                (2020,0.95),(2030,0.95),(2040,1) PRISM- 30 to 64
                [(1990,0)-(2040,0.08)],(1990,0.015),(2000,0.015),(2010,0.02),(202
                0,0.025),(2030,0.03),(2040,0.025)
                [(1980,0)-(2040,2)],(1980,1),(1990,1.05),(2000,1.1),(2010,1),(202
                0,0.95),(2030,0.9),(2040,1)
                [(1980,0)-(2040,2)],(1980,1),(1990,1),(2000,1.05),(2010,1),(2020,
                0.9),(2030,0.9),(2040,0.95)
                [(1980,0)-(2040,2)],(1980,1),(1990,1),(2000,1),(2010,1),(2020,1),
                (2030,1),(2040,1)

Real M0 Fraction=
        ZIDZ(RealPrevM0,RealPrevM0plusM1)
Units: dmnl
Fract of Real M0/(M0+M1). percent real prevalence of M0, out of
                100%. should be around 80%

Real M1 Fraction=
        1-Real M0 Fraction
Units: dmnl
Fract of Real M1/(M0+M1). percent real prevalence of M0, out of
                100%. should be around 80%

"Real PCa Death Rate (people/yr)"=
        1
Units: dmnl

Real PCa Incidence=
        SUM("Real PCa Incidence, by age"[Age!])
Units: People/year

"Real PCa Incidence, by age"[Age]=
        SUM(AsxInci[Age,Grade!])+SUM(AsxInci2[Age,Grade!])+SUM(AsxInci3[Age,Grade!
])
Units: People/year

Real PCa Prevalence=
        SUM(Real PCa Prevalence by age[Age!])
Units: People

Real PCa Prevalence by age[Age]=
        SUM("Real PCa Prevalence by age, grade Primary treatment only"[Age,Grade!]
)
Units: People

"Real PCa Prevalence by age, grade Primary treatment only"[Age,Grade]=
        Ux LocoRegional M0[Age,Grade]+Ux Distant M1[Age,Grade]+Total Diagnosed by age grade

[Age,Grade]+Nr Treated by age grade treatment[Age,Grade,ActiveSurveillance]
+Nr Treated by age grade treatment[Age,Grade,RadioTheraphy]
Units: People
INDOLENT DISEASE IS INCLUDED. CALCULATE PREVALENCE W/O INDOLENT
                DISEASE (PROGRESSIVE DISEASE) SEPERATELY? JOHN: Assume RP's are
                treated

Real PCa Prevalence by grade[Grade]=
        SUM("Real PCa Prevalence by age, grade Primary treatment only"[Age!,Grade]
)
Units: People

Real Progressive PCa Prevalence=
        SUM(Real Progressive PCa Prevalence by grade[Grade!])
Units: People
INDOLENT DISEASE IS INCLUDED. CALCULATE PREVALENCE W/O INDOLENT
                DISEASE (PROGRESSIVE DISEASE) SEPERATELY? JOHN: Assume RP's are
                treated

Real Progressive PCa Prevalence by age grade[Age,Grade]=
        "Real PCa Prevalence by age, grade Primary treatment only"[Age,High]+"Real PCa Prevalence by age, grade
Primary treatment only"
[Age,Low]
Units: People
INDOLENT DISEASE IS INCLUDED. CALCULATE PREVALENCE W/O INDOLENT
                DISEASE (PROGRESSIVE DISEASE) SEPERATELY? JOHN: Assume RP's are
                treated

Real Progressive PCa Prevalence by grade[Grade]=
        SUM(Real Progressive PCa Prevalence by age grade[Age!,Grade])
Units: People
INDOLENT DISEASE IS INCLUDED. CALCULATE PREVALENCE W/O INDOLENT
                DISEASE (PROGRESSIVE DISEASE) SEPERATELY? JOHN: Assume RP's are
                treated
RealPrev=SUM(RealPrevM0 by grade[Grade!])+SUM(RealPrevM1 by grade[Grade!])
Units: People
RealPrevM0=SUM(RealPrevM0 by grade[Grade!])
Units: People
Real prevalence of M0-locoregional dosease. Subtract Ux disease to find estimated prevalence
RealPrevM0 by grade[Grade]=SUM(CxM0 age grade[Age!,Grade])+SUM(SxM0 age grade[Age!,Grade])+SUM(TxM0[Age
!,Grade,Treatment!])+SUM(UxM0[Age!,Grade])
Units: People
Real prevalence of M0-locoregional dosease. Subtract Ux disease
                to find estimated prevalence-- subtract treated with radical
                prostatectomy
RealPrevM0plusM1=RealPrevM0+RealPrevM1
Units: People
Real prevalence of M0-locoregional dosease. Subtract Ux disease
                to find estimated prevalence
RealPrevM1=SUM(RealPrevM1 by grade[Grade!])
Units: People
Real prevalence of M1-distant disease. Subtract Ux disease to
                find estimated prevalence of distant disease
RealPrevM1 by grade[Grade]=SUM(CxM1 age grade[Age!,Grade])+SUM(SxM1 age grade[Age!,Grade])+SUM(TxM1[Age
!,Grade,Treatment!])+SUM(UxM1[Age!,Grade])+SUM(Tx SxM0M1[Age!,Grade,Treatment
!])+SUM(Tx CxM0M1[Age!,Grade,Treatment!])
Units: People
Real prevalence of M1-distant disease. Subtract Ux disease to
                find estimated prevalence of distant disease
Recommended Age to Screen=
        50

Units: dmnl
50
Recommended Biopsy Threshold=4
Units: dmnl
Recommended Starting Age R[group]= INTEG (
        Change in R[group],
                INIT R[group])
Units: Ages

Ref Yield to RD=
        1e-006
Units: 1/$
Normal innovation fraction. Under normal conditions, the model
                will generate a 4% per year increase in Technology. We assume a
                positive feedback structure to exist for this exponential
                growth, which has both theoretical and empirical
                justifications...

Reference Prospects=
        0.01
Units: dmnl

Relative Influence of Advocacy Groups=
        1
Units: dmnl
Dimensionless relative strength of advocacy groups--base case
                value is 1--strength of advocacy groups in 1975 stock of PP.
                which changes between 0-1

reldfTxforM0[Treatment]=
        1,0.2,0.1
Units: dmnl
treatment efficincy: we assume no improvements in survival
                during the PSA era due to treatment. PCSIM page 12. Relative
                death fraction of Treated M0 patients, relative to without
                treatment death fraction--indicates treatment efficacy. also
                changes by age, more efficient in younger men? Grade and
                treatment specific, i.e. treatment is more effective at lower
                grades. Estimate on SEER survival curves by stage (almost 100%
                at 5 years for loco-regional cases)

reldfTxforM0M1[Treatment]=
        1,0.9,0.8
Units: dmnl
1,0.9,0.8 Relative death fraction of Treated M0 patients,
                relative to without treatment death fraction--indicates
                treatment efficacy. Grade and treatment specific, i.e. treatment
                is more effective at lower grades. Estimate on SEER survival
                curves by stage (almost 100% at 5 years for loco-regional cases)

reldfTxforM1[Treatment]=
        1,0.6,0.2
Units: dmnl
treatment efficincy: we assume no improvements in survival
                during the PSA era due to treatment. PCSIM page 12. Relative
                death fraction of Treated M1 patients, relative to without
                treatment death fraction--indicates treatment efficacy. Grade
                and treatment specific, i.e. treatment is more effective at
                lower grades. Treatment types= AS, RT, RP

relfollowup=

279

1/4
Units: dmnl

relMxTxM0[Treatment]=
        1,0.3,0.09
Units: dmnl
About three percent of patients on surveillance had metastasis
                by a median of seven years after diagnosis:
                https://www.sciencedaily.com/releases/2016/04/160411134614.htm
                1,0.3,0.09 Relative metastasis rate of loco-regional disease
                after TREATMENT. Ref: Underwood et al., 2012 metastasis hazard:
                b=0.006 MCRPR= Mayo Clinic Radical Prostatectomy Registry, for
                patients under treatment. e=0.069 for patients not diagnosed
                (Ghani et al., Scardino et al).

Repeat PSA Rate=
        Repeat PSA Screening Rate/Number of Tests Per Person/Total Popn*100
Units: 1/year

Repeat PSA Screening Data:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'L16')
Units: 1/year

Repeat PSA Screening Data Normalized=
        Repeat PSA Screening Data/27*Max Adoption Fraction
Units: 1/year

Repeat PSA Screening Rate=
        PSA Screening Rate-First PSA Screening Rate
Units: tests/year

Reported Crude PCa Incidence by age[Age]=
        Reported PCa Incidence rate by age[Age]*per100000men
Units: People/year

Reported PCa Incidence=
        SUM(Reported PCa Incidence by age[Age!])
Units: People/year
should be positive before screening starts

Reported PCa Incidence by age[Age]=
        SUM(cxRatePCa[Age,Grade!])+SUM(sxRatePCa[Age,Grade!])
Units: People/year
Cancer incidence rate is the sum of screen and clinically
                detected cancer rates

Reported PCa Incidence M0=
        SUM(sxM0[Age!,Grade!])+SUM(cxM0[Age!,Grade!])
Units: People/year
Cancer incidence rate is the sum of screen and clinically
                detected cancer rates

Reported PCa Incidence M0 per 100thou=
        Reported PCa Incidence M0/Total Popn Time Series ALL AGES*per100000men
Units: People/year
Cancer incidence rate is the sum of screen and clinically
                detected cancer rates

Reported PCa Incidence M1=
        SUM(cxM1[Age!,Grade!])+SUM(sxM1[Age!,Grade!])
Units: People/year

Cancer incidence rate is the sum of screen and clinically
                detected cancer rates

Reported PCa Incidence M1 per 100thou=
        Reported PCa Incidence M1/Total Popn Time Series ALL AGES*per100000men
Units: People/year
Cancer incidence rate is the sum of screen and clinically
                detected cancer rates

Reported PCa Incidence rate by age[Age]=
        Reported PCa Incidence by age[Age]/Total Popn by age[Age]
Units: 1/year
Cancer incidence rate is the sum of screen and clinically
                detected cancer rates Cowen et al, 1993. table1- column 2 compare

Reported PCa Prevalence=
        SUM(Reported PCa Prevalence by age[Age!])
Units: People
Cancer survivors, or prevalence of PCa: In 2011, there were an
                estimated 2,707,821 men living with prostate cancer in the
                United States. 1,380,000 in 2010. Includes indolent disease, as
                we dont know if it was indolent or not. Assuming constant
                incidence, survival, and cost, projection is 13.8 and 18.1
                million cancer survivors in 2010 and 2020, respectively, with
                associated costs of cancer care of 124.57 and 157.77 billion
                2010 US dollars.
                http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
                survivor: any person diagnosed with cancer, from the time of
                initial diagnosis until his or her death.
                http://costprojections.cancer.gov/cancer.prevalance.html

"Reported PCa Prevalence (Nr Ever Diagnosed) by age grade"[Age,Grade]=
        Nr Treated by age grade[Age,Grade]+Total Diagnosed by age grade[Age,Grade]
Units: People
Includes indolent disease, as we dont know if it was indolent or
                not.1.38e+007 in 2010. Assuming constant incidence, survival,
                and cost, projection is 13.8 and 18.1 million cancer survivors
                in 2010 and 2020, respectively, with associated costs of cancer
                care of 124.57 and 157.77 billion 2010 US dollars.
                http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
                survivor: any person diagnosed with cancer, from the time of
                initial diagnosis until his or her death.
                http://costprojections.cancer.gov/cancer.prevalance.html

Reported PCa Prevalence by age[Age]=
        SUM("Reported PCa Prevalence (Nr Ever Diagnosed) by age grade"[Age,Grade!]
)
Units: People
Includes indolent disease, as we dont know if it was indolent or
                not.1.38e+007 in 2010. Assuming constant incidence, survival,
                and cost, projection is 13.8 and 18.1 million cancer survivors
                in 2010 and 2020, respectively, with associated costs of cancer
                care of 124.57 and 157.77 billion 2010 US dollars.
                http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
                survivor: any person diagnosed with cancer, from the time of
                initial diagnosis until his or her death.
                http://costprojections.cancer.gov/cancer.prevalance.html

Reported PCa Prevalence by grade[Grade]=
        SUM("Reported PCa Prevalence (Nr Ever Diagnosed) by age grade"[Age!,Grade]
)

Units: People
Includes indolent disease, as we dont know if it was indolent or
not.1.38e+007 in 2010. Assuming constant incidence, survival,
and cost, projection is 13.8 and 18.1 million cancer survivors
in 2010 and 2020, respectively, with associated costs of cancer
care of 124.57 and 157.77 billion 2010 US dollars.
http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
survivor: any person diagnosed with cancer, from the time of
initial diagnosis until his or her death.
http://costprojections.cancer.gov/cancer.prevalance.html

Reported PCa Prevalence or Nr Ever Diagnosed by age[Age]=
SUM("Reported PCa Prevalence (Nr Ever Diagnosed) by age grade"[Age,Grade!]
)
Units: People
Includes indolent disease, as we dont know if it was indolent or
not.1.38e+007 in 2010. ABOUT 3 MILLION FOR PCa. Assuming
constant incidence, survival, and cost, projection is 13.8 and
18.1 million cancer survivors in 2010 and 2020, respectively,
with associated costs of cancer care of 124.57 and 157.77
billion 2010 US dollars.
http://jnci.oxfordjournals.org/content/103/2/117.long. Cancer
survivor: any person diagnosed with cancer, from the time of
initial diagnosis until his or her death.
http://costprojections.cancer.gov/cancer.prevalance.html

Rescreened and Negative[Age]=
At Risk and Screened FP[Age]/TimetoRecall*PofTminusDminus*BiopCompM0*Screen Switch
Units: People/year
rescreening interval may be less than that of the initial
screening interval

retxCxM1[Age,Grade,Treatment]=
Tx CxM0M1[Age,Grade,Treatment]/TimeToAct
Units: People/year

retxSxM1[Age,Grade,Treatment]=
Tx SxM0M1[Age,Grade,Treatment]/TimeToAct
Units: People/year

"ROC for PSA Etzioni et al., 2004"=
"Table ROC for PSA Etzioni et al., 2004"(FP)
Units: dmnl

"ROC for PSA Jacobsen et al., 1996 age 50-59"=
"Table ROC for PSA Jacobsen et al., 1996 age 50-59"(FP)
Units: dmnl

"ROC for PSA Jacobsen et al., 1996 age 60-69"=
"Table ROC for PSA Jacobsen et al., 1996 age 60-69"(FP)
Units: dmnl

"ROC for PSA Jacobsen et al., 1996 age 70-79"=
"Table ROC for PSA Jacobsen et al., 1996 age 70-79"(FP)
Units: dmnl

"ROC for PSA Jacobsen et al., 1996 D+"=
"Table ROC for PSA Jacobsen et al., 1996 AUC=0.83"(FP)
Units: dmnl

"ROC for PSA Jacobsen et al., 1996"=

"Table ROC for PSA Jacobsen et al., 1996 AUC=0.72"(FP)
Units: dmnl

"ROC for PSA Thompson et al., 2005"=
        "Table ROC for PSA, Thompson et al., 2005 AUC=0.678"(FP)
Units: dmnl

"ROC for PSA, Ahn et al."=
        "Table ROC for PSA, Ahn et al. 2014 AUC=0.577"(FP)
Units: dmnl

"ROC for PSA, Ferro et al., 2015"=
        "Table ROC for PSA, Ferro et al., 2015"(FP)
Units: dmnl

"ROC for PSA, Steuber et al., 2008"=
        "Table ROC for PSA, Steuber et al., 2008"(FP)
Units: dmnl

"ROC for PSA, Thompson et al., 2005 Gleason>7 or no PCa"=
        "Table ROC for PSA, Thompson et al., 2005 Gleason>7 or no PCa"(FP)
Units: dmnl

"ROC for PSA, Thompson et al., 2005 Gleason>8 or no PCa"=
        "Table ROC for PSA, Thompson et al., 2005 Gleason>8 or no PCa"(FP)
Units: dmnl

"ROC for PSA, Underwood et al. 2012"=
        "Table ROC for PSA, Underwood et al. 2012"(FP)
Units: dmnl

SAVEPER =
    TIME STEP
Units: year [0,?]
The frequency with which output is stored.

scRateAtRisk[Age]=
        At Risk Never Screened Pop[Age]/TimeBtwSx*Current Screened Fraction[Age]
Units: People/year
screen on deleted

scRateAtRiskFP[Age]=
        At Risk and Screened FP[Age]/TimeBtwSx*Current Screened Fraction[Age]
Units: People/year
screen on deleted

scRateAtRiskTN[Age]=
        At Risk and Screened TN[Age]/TimeBtwSx*Current Screened Fraction[Age]
Units: People/year
screen on deleted

scRateCxM0[Age,Grade]=
        Cx LocoRegional M0[Age,Grade]*Fraction F/TimeBtwSx*Current Screened Fraction
[Age]
Units: People/year
screen on deleted

scRateCxM1[Age,Grade]=
        Cx Distant M1[Age,Grade]*Fraction F/TimeBtwSx*Current Screened Fraction[Age
]
Units: People/year

283

screen on deleted

scRateSxM0[Age,Grade]=
         Sx LocoRegional M0[Age,Grade]*Fraction F/TimeBtwSx*Current Screened Fraction
[Age]
Units: People/year
screen on deleted

scRateSxM1[Age,Grade]=
         Sx Distant M1[Age,Grade]*Fraction F/TimeBtwSx*Current Screened Fraction[Age
]
Units: People/year
screen on deleted

scRateTxCxM0[Age,Grade,Treatment]=
         Tx CxM0[Age,Grade,Treatment]*Fraction F/TimeBtwSx*Current Screened Fraction
[Age]
Units: People/year
screen on deleted

scRateTxCxM0M1[Age,Grade,Treatment]=
         Tx CxM0M1[Age,Grade,Treatment]*Fraction F/TimeBtwSx*Current Screened Fraction
[Age]
Units: People/year
screen on deleted

scRateTxSxM0[Age,Grade,Treatment]=
         Tx SxM0[Age,Grade,Treatment]*Fraction F/TimeBtwSx*Current Screened Fraction
[Age]
Units: People/year
screen on deleted

scRateTxSxM0M1[Age,Grade,Treatment]=
         Tx SxM0M1[Age,Grade,Treatment]*Fraction F/TimeBtwSx*Current Screened Fraction
[Age]
Units: People/year
screen on deleted

scRateUxM0[Age,Grade]=
         Ux LocoRegional M0[Age,Grade]/TimeBtwSx*Current Screened Fraction[Age]
Units: People/year
screen on deleted

scRateUxM1[Age,Grade]=
         Ux Distant M1[Age,Grade]/TimeBtwSx*Current Screened Fraction[Age]
Units: People/year
screen on deleted

Screen Eligible Fraction[Age]=
         Standard Eligibility Fraction*Effect of Stopping Age on Eligible Fraction[
Age]*Effect of Starting Age on Eligible Fraction[Age]
Units: dmnl

Screen On=
         IF THEN ELSE(Time<Screening Start Year,0,Screen Switch)
Units: dmnl

Screen Switch=
         1
Units: dmnl [0,1,0.5]
IF THEN ELSE(Time>2020, 0 , 1)

Screened and FP Rate[Age]=
        At Risk and Screened TN[Age]/TimeBtwSx*(1-Specificity)*Screen Switch
Units: People/year
secondary screening, they are actually at higher risk for
                getting a second false positive!

Screening Coverage=
        1
Units: dmnl
PSA screening coverage by Medicare started in 2000:
                http://healthcaredelivery.cancer.gov/seermedicare/considerations/
                testing.html It is important to note that it is difficult to
                distinguish screening from diagnostic tests. Inclusion of only
                the screening codes will result in a significant undercount of
                true screening rates. In addition, tests that were not billed to
                Medicare will not be captured in these data. Examples of this
                are mammograms performed in a mobile clinic as part of a
                community outreach or PSA tests done in community settings.

Screening Rate of Dx[Age]=
        (SUM(scRateCxM0[Age,Grade!])+SUM(scRateCxM1[Age,Grade!])+SUM(scRateSxM0[Age
,Grade!])+SUM(scRateSxM1[Age,Grade!]))*Number of Tests Per Person
Units: tests/year

Screening Rate of Tx[Age,Treatment]=
        (SUM(scRateTxCxM0[Age,Grade!,Treatment])+SUM(scRateTxCxM0M1[Age,Grade!,Treatment
])+SUM(scRateTxSxM0M1[Age,Grade!,Treatment])+SUM(scRateTxSxM0[Age,Grade!,Treatment
]))*Number of Tests Per Person
Units: tests/year

Screening Rate of Ux[Age,Grade]=
        (scRateUxM0[Age,Grade]+scRateUxM1[Age,Grade])*Number of Tests Per Person
Units: tests/year
total number of tests for men with disease, both indolent and
                progressive, during the simulation time horizon before the
                disease gets detected? how about after?

Screening Rate wo Disease[Age]=
        (scRateAtRisk[Age]+scRateAtRiskFP[Age]+scRateAtRiskTN[Age])*Number of Tests Per Person
Units: tests/year
total number of tests for men without disease, both indolent and
                progressive, during the simulation time horizon

Screening Start Year=
        1985
Units: year [1980,1990,1]
screening practice starts in 1987-88

SDx M0 Ind=
        0
Units: People
Since this is latent disease by definition which wouldnt have
                been detected otherwise during lifetime (wouldnt manifest itself
                clinically), it represents overdiagnosis--diagnosis with a
                cancer not destined to cause symptoms or death (Welch and Black,
                2010).

Sector Info=
        1
Units: dmnl

Generating, disseminating, implementing evidence (PCORI)
Evidence-based core.

SEER Pop Data=
1
Units: dmnl
http://seer.cancer.gov/popdata/

SEER PSA info=
1
Units: dmnl
PSA values are removed from SEER datasets:
http://seer.cancer.gov/data/psa-values.html

SEER Stage Distribution=
1
Units: dmnl
2003-2012 data: 80% localized, 11.4% regional, 4.2% distant,
4.3% unstaged.
http://seer.cancer.gov/seerstat/variables/seer/ajcc-stage/ Link:
http://seer.cancer.gov/faststats/selections.php?run=runit&output=
1&data=1&statistic=12&year=201504&race=1&sex=2&age=1&series=cance
r&cancer=66

selection rate=
1
Units: dmnl
As the selection rate (the percentage of screened men who are
diagnosed as positive) increases, the false negative proportion
drops, but the false positive proportion increases.

Sensitivity=
"True Pos Rate (TPR)"[d1]
Units: dmnl
Endogeneous sensitivity of the screening test. true
positives/[true positives+false negatives]. In signal detection
theory, overall performance depends both on accuracy (otherwise
known as 'sensitivity') of judgment and on the threshold
(otherwise known as 'bias'). The standard measures of
sensitivity and bias (e.g., Macmillan & Creelman, 2005) assume
normality. --Stewart, 2012.

Sensitivity of HBR to Utility=
100
Units: dmnl

SensM0=
0.8
Units: dmnl
Sensitivity loco-regional (M0) disease--(make it endogeneous)
Can be subscripted by grade (1- High, 2- Low, 3- Indolent) The
parameters for psa test sensitivity are stage specific because
the sens of a test primarily depends on the size of the t8umor.
http://www.ncbi.nlm.nih.gov/pubmed/20142584--pg 1. wever et al.
2009. the actual observed incidence was reproduced by assuming a
substantially lower PSA test sensitivity in the United States
than in ERSPC–Rotterdam. For example, for nonpalpable local-
or regional-stage cancers (ie, stage T1M0), the estimates of PSA
test sensitivity were 0.26 in the United States vs 0.94 in
ERSPC–Rotterdam. We conclude that the efficacy of PSA
screening in detecting prostate cancer was lower in the United

States than in ERSPC–Rotterdam

SensM1=
   1
Units: dmnl
Sensitivity of distant-metastasized (M1) disease, take as 1.

"Sigma D+"=
   0.8
Units: dmnl
0.7 Standard deviation of the distribution of the test outcome
            for the healthy (D+) population. UNKNOWN, but should be higher
            than STDEV(D-). used to be 1.05

"Sigma D-"=
   0.5
Units: dmnl
Standard deviation of the distribution of the test outcome for
            the healthy (D-) population. UNKNOWNN.used to be 0.16, 0.3,
            0.85, 0.6

Slackfolks=
            Total Popn-Calculated Total Popn
Units: People

"Slope D+"=
   0.012
Units: 1/Ages
0.011 Rate of change in prevalance per year, allows adjustments
            to real underlying prevalance of PCa, which is estimated by
            autopsy series. Jahn et al,2015 gives prevalance based on race,
            difference is big (US white vs. US black)--ESTIMATE:
            1.38/100=0.0138 according to Sanchez Chapado et al., 2003.
            Sanchez chapado et al/, 2003--slope for AA and CA, african
            american and caucasian americans is 1.38. R2==0.96, for CM 0.75.
            Fig. 3. Comparison of the prevalence of CaP in Caucasian
            Mediterranean (CM) men, Caucasian-American (CA) men, and
            African-American(AA)men

Sojourn and Lead Time Data=
   1
Units: dmnl
lead mean 7 years, sojourn mean 13.5 years
            http://www.ncbi.nlm.nih.gov/pubmed/20530126 page 715.

Specificity=
            1-"False Pos Rate (FPR)"[d1]
Units: dmnl
Specificity of the test result. true negatives/[true
            negatives+false positives]) =d/(d+c)

SpecsM0=
   0.4
Units: dmnl
Sensitivity loco-regional (M0) disease--make endogeneous

Standard Eligibility Fraction=
   1
Units: dmnl
maximum eligibility fraction, or standard eligibility
            fraction--> john: reference addressable market

State Cancer Profiles=
        1
Units: dmnl
http://statecancerprofiles.cancer.gov/
                http://statecancerprofiles.cancer.gov/data-topics/screening-risk-
                factors.html
                http://statecancerprofiles.cancer.gov/map/map.noimage.php

StoppingAge=
        75
Units: Ages
in 2008 USPSTF says dont screen men over 75. general practice
                now is not to screen men over a certain age, that age decreased
                to 65's almost, from 75-80

StrengthEffExtPonT=
        0
Units: dmnl
Sensitivity of External Pressure's effect on Threshold T

StrengthEffofHBRonT=
        0.3
Units: dmnl
Sensitivity of BHR ratio's effect on PSA Threshold T.

Survival=
        1
Units: dmnl
In the absence of curative treatment, a cancer diagnosed at the
                localized stage before the age of 65 years is associated with a
                specific survival of less than 30%. The median survival of
                metastatic prostatic cancer is 2 to 3 years.
                http://www.ncbi.nlm.nih.gov/pubmed/9410329

Survival time M0 cases[Grade]=
        37.8,400,1e+008
Units: year
Estimate on SEER survival curves by stage (localized and
                regional almost 100% at 5 years). 400 for localized, 37.8 for
                regional cases. In the absence of curative treatment, a cancer
                diagnosed at the localized stage before the age of 65 years is
                associated with a specific survival of less than 30%. The median
                survival of metastatic prostatic cancer is 2 to 3 years.
                http://www.ncbi.nlm.nih.gov/pubmed/9410329

Survival time M1 cases[Grade]=
        4.95,5.5,1e+008
Units: year
Estimate on SEER survival curves by stage

Switch R[group]=
        1,1
Units: dmnl

Switch T[group]=
        1,1
Units: dmnl

Sx Distant M1[Age,Grade]= INTEG (
        mxSxM0[Age,Grade]+sxM1[Age,Grade]-SUM(txSxM1[Age,Grade,Treatment!])-XXocSxM1

[Age,Grade]-XXpcSxM1[Age,Grade]+EnterAgeSxM1

[Age,Grade]-LeaveAgeSxM1[Age,Grade]+ImmSxM1[Age,Grade],

0)

Units: People
Screen detected distant-metastasized cancer (M1). M1 corresponds

to Clinical stage D, lymph node involvement or distant

metastases. Represents distant cancer based on SEER. initial

value is zero, no screening at the start of the simulation

Sx LocoRegional M0[Age,Grade]= INTEG (

sxM0[Age,Grade]-mxSxM0[Age,Grade]-SUM(txSxM0[Age,Grade,Treatment!])-XXocSxM0
[Age,Grade]-XXpcSxM0[Age,Grade]+EnterAgeSxM0

[Age,Grade]-LeaveAgeSxM0[Age,Grade]+ImmSxM0[Age,Grade],

0)

Units: People
Screen detected locoregional cancer (M0). initial value is zero,

no screening at the start of the simulation

Sx M0 High=

0

Units: People
Clinical stage A, Clinically localized and nonpalpable on DRE.

Represents local (stage I) cancer based on SEER. Clinically

localized cancers include T1 and T2 tumors. SEER data assigns

cancer stage using clinical and pathological data. Hoffman 2003,

refs 11-13. The SEER Program collects data on cancer incidence,

treatment, and mortality from cancer registries that cover

approx. 14% of the US population, and believed to be reasonably

representative o the US. Nat. Canc. Inst. SEER program.

Available at: http://seer.cancer.gov/ T1 tumors are defined as

confined to the prostate with a normal DRE and no positive

scans, or evidence of metastasis. T2 tumors are defined as

comfined to the prostate with abnormal or suspicious DRE's, but

no positive scans or evidence of metastasis. (Hoffman et al.,

2003).Localized: An invasive malignant neoplasm confined

entirely to the organ of origin.

Sx M1 High=

0

Units: People
Clinical stage B, Clinically localized but palpable on DRE.

Represents local (stage II) cancer based on SEER. T1 tumors are

defined as confined to the prostate with a normal DRE and no

positive scans, or evidence of metastasis. T2 tumors are defined

as comfined to the prostate with abnormal or suspicious DRE's,

but no positive scans or evidence of metastasis. (Hoffman et

al., 2003).

sxM0[Age,Grade]=

Ux LocoRegional M0[Age,Grade]*Screen Switch*Current Screened Fraction[Age]
/TimeBtwSx*EffectiveTestSensM0[Age]
Units: People/year
Screen detection rate of local-regional, low-grade (M0G0)

disease, dont confuse with screening rate. Diagnosis rate by

screening is indicated as sx.

SxM0 age grade[Age,Grade]=

Sx LocoRegional M0[Age,Grade]
Units: People
"Sx M0-Ind"+"Sx M0-Low"

sxM1[Age,Grade]=
        Ux Distant M1[Age,Grade]*Screen Switch*Current Screened Fraction[Age]/TimeBtwSx
*EffectiveTestSensM1
Units: People/year
Screen detection rate of metastasized, low-grade (M1G0) disease,
               dont confuse with screening rate

SxM1 age grade[Age,Grade]=
        Sx Distant M1[Age,Grade]
Units: People

sxRatePCa[Age,Grade]=
        sxM0[Age,Grade]+sxM1[Age,Grade]
Units: People/year
screen detected cancer rate per year

sxRatePCa by age[Age]=
        SUM(sxRatePCa[Age,Grade!])
Units: People/year

sxRateTotal=
        SUM(sxRatePCa[Age!,Grade!])
Units: People/year

"Table Age vs D+ Carter, 1990 Japan Histological"(
        [(0,0)-(100,1)],(25,0),(30.003,0.00613282),(40,0.0195836),(50,0.0844109),(
60,0.151684),(70,0.260475),(80,0.398689),(100,0.3987))
Units: dmnl
Carter-- from Cowen, 1994 Markov model The pathologic prevalance
               of PCa per 100.000 US males at a given age. literature values
               derived from Carter, 1990. Age-specific prevalance of
               histological PCa, by plotting prevalance as a function of host
               age (time)

"Table Age vs D+ Carter, 1990 US Histological"(
        [(0,0)-(100,1)],(25,0),(30,0.0097),(35,0.014),(40,0.0203),(45,0.0295),(50,
0.0428),(55,0.0621),(60,0.09),(65,0.1306),(70,0.1895),(75,0.2749),(80,0.3988
),(100,0.3988))
Units: dmnl
Carter-- from Cowen, 1994 Markov model. The pathologic
               prevalance of PCa per 100.000 US males at a given age.
               literature values derived from Carter, 1990. Age-specific
               prevalance of histological PCa, by plotting prevalance as a
               function of host age (time)

"Table Age vs D+ Carter, 1990 US Male Clinical"(
        [(0,0)-(100,0.1)],(25,0),(50,0),(55,0.00123712),(60,0.00353735),(65,0.00772406
),(70,0.0140747),(75,0.0234018),(80,0.032992),(100,0.03299))
Units: dmnl

"Table Age vs D+ Guileyardo, 1980 US Blacks"(
        [(25,0)-(100,1)],(25,0.2),(52.5,0.2),(65,0.344),(75,0.442),(100,0.442))
Units: dmnl
US blacks, 1980. n=207, mean 31.4%

"Table Age vs D+ Guileyardo, 1980 US Whites"(
        [(25,0)-(100,1)],(25,0.23),(52.5,0.23),(65,0.316),(75,0.407),(100,0.407))
Units: dmnl
us whites. 1980 n=293

"Table Age vs D+ Haas et al., 2007-all PCa"(

[(25,0)-(90,1)],(25,0.04),(30,0.0461538),(34.6531,0.0564103),(40.0408,0.0769231
),(43.8367,0.0974359),(50.6939,0.141026),(55.7143,0.184615),(61.102,0.241026
),(66.1225,0.307692),(70.898,0.371795),(75.3061,0.438462),(81.7959,0.548718
),(86.9388,0.628205),(88.6531,0.653846))
Units: dmnl
http://jnci.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=1789
                5474

"Table Age vs D+ Haas et al., 2007-clinically significant"(
        [(25,0)-(90,1)],(25,0),(30,0.0025641),(34.1633,0),(38.0816,0.00769231),(43.5918
,0.0025641),(48.4898,0.0102564),(54.4898,0.0230769),(59.0204,0.0410256),(63.6735
,0.0666667),(67.9592,0.120513),(71.6327,0.166667),(75.1837,0.235897),(78.3673
,0.312821),(82.1633,0.420513),(85.2245,0.520513),(87.9184,0.605128),(89.0204
,0.635897))
Units: dmnl
http://jnci.oxfordjournals.org/cgi/pmidlookup?view=long&pmid=1789
                5474

"Table Age vs D+ Jahn et al., 2015 Asian"(
        [(0,0)-(100,1)],(25,0.0209836),(35,0.00786885),(45,0.0288525),(55,0.0813115
),(65,0.146885),(75,0.212459),(85,0.288525),(100,0.2885))
Units: dmnl
Prostate cancer risk as a function of age, Jahn et al., 2015 Int
                J of Cancer.
                http://onlinelibrary.wiley.com/doi/10.1002/ijc.29408/abstract
                http://www.uptodate.com/contents/screening-for-prostate-cancer
                Although about 80 percent of detected cancers are considered
                clinically important based on tumor size and grade [157], these
                are relatively crude prognostic markers. Autopsy series in men
                who died from other causes have shown a 30 to 45 percent
                prevalence of prostate cancer in men in their fifties and an 80
                percent prevalence in men in their seventies [158-160]. Jahn et
                al., 2015.

"Table Age vs D+ Jahn et al., 2015 US Black"(
        [(0,0)-(100,1)],(25,0.0708197),(35,0.302951),(45,0.352787),(55,0.461639),(
65,0.472131),(75,0.504918),(100,0.5049))
Units: dmnl
Prostate cancer risk as a function of age, Jahn et al., 2015 Int
                J of Cancer.
                http://onlinelibrary.wiley.com/doi/10.1002/ijc.29408/abstract
                http://www.uptodate.com/contents/screening-for-prostate-cancer
                Although about 80 percent of detected cancers are considered
                clinically important based on tumor size and grade [157], these
                are relatively crude prognostic markers. Autopsy series in men
                who died from other causes have shown a 30 to 45 percent
                prevalence of prostate cancer in men in their fifties and an 80
                percent prevalence in men in their seventies [158-160]. Jahn et
                al., 2015.

"Table Age vs D+ Jahn et al., 2015 US White-European"(
        [(25,0)-(100,1)],(25,0.0413),(35,0.1573),(45,0.2341),(55,0.2243),(65,0.2926
),(75,0.3593),(85,0.4761),(100,0.4761))
Units: dmnl
Prostate cancer risk as a function of age, Jahn et al., 2015 Int
                J of Cancer.
                http://onlinelibrary.wiley.com/doi/10.1002/ijc.29408/abstract
                http://www.uptodate.com/contents/screening-for-prostate-cancer
                Although about 80 percent of detected cancers are considered
                clinically important based on tumor size and grade [157], these
                are relatively crude prognostic markers. Autopsy series in men

291

who died from other causes have shown a 30 to 45 percent
prevalence of prostate cancer in men in their fifties and an 80
percent prevalence in men in their seventies [158-160]. Jahn et
al., 2015.

"Table Age vs D+ Rebbeck et al., 2014 African Descent"(
          [(0,0)-(100,1)],(25,0.016),(35,0.355),(45,0.247),(55,0.39),(65,0.567),(100
,0.567))
Units: dmnl
Prostate cancer risk as a function of age.
                    http://www.ncbi.nlm.nih.gov/pubmed/25347377 page 7- panel 3.
                    mean=26.2%

"Table Age vs D+ Rebbeck et al., 2014 Asian Descent"(
          [(25,0)-(95,1)],(25,0),(35,0.04),(45,0.063),(55,0.173),(65,0.177),(75,0.254
),(85,0.332),(95,0.5))
Units: dmnl
Prostate cancer risk as a function of age.
                    http://www.ncbi.nlm.nih.gov/pubmed/25347377 page 7- panel 1.
                    mean=19.9%

"Table Age vs D+ Rebbeck et al., 2014 European Descent"(
          [(0,0)-(95,1)],(25,0.05),(35,0.084),(45,0.15),(55,0.269),(65,0.333),(75,0.354
),(85,0.49),(95,0.911))
Units: dmnl
Prostate cancer risk as a function of age.
                    http://www.ncbi.nlm.nih.gov/pubmed/25347377 page 7- panel 2.
                    mean=26.7%

"Table Age vs D+ Sakr et al., 1993 US White"(
          [(25,0)-(100,0.9)],(25,0.08),(35,0.31),(45,0.37),(55,0.44),(65,0.65),(75,0.83
),(100,0.83))
Units: dmnl
REAL D+ is UNKNOWN, we use estimates coming from autopsy series.
                    http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2706483/ Haas et
                    al., 2008. The Worldwide Epidemiology of Prostate Cancer:
                    Perspectives from Autopsy Studies--DATA for US White Sakr WA,
                    Haas GP, Cassin BF, Pontes JE, Crissman JD. The frequency of
                    carcinoma and intraepithelial neoplasia of the prostate in young
                    male patients. J Urol. 1993;150(2 Pt 1):379-385. [PubMed] Table
                    age groups 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90

"Table Age vs D+ Sakr et al., 1993. US Black"(
          [(25,0)-(100,0.9)],(25,0.08),(35,0.31),(45,0.43),(55,0.46),(65,0.7),(75,0.81
),(100,0.81))
Units: dmnl
REAL D+ is UNKNOWN, we use estimates coming from autopsy series.
                    http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2706483/ Haas et
                    al., 2008. The Worldwide Epidemiology of Prostate Cancer:
                    Perspectives from Autopsy Studies--DATA for US Black Sakr WA,
                    Haas GP, Cassin BF, Pontes JE, Crissman JD. The frequency of
                    carcinoma and intraepithelial neoplasia of the prostate in young
                    male patients. J Urol. 1993;150(2 Pt 1):379-385. [PubMed] Table
                    age groups 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90

"Table Age vs D+ Sakr et al., 1994 African American"(
          [(0,0)-(100,1)],(25,0.03),(35,0.26),(45,0.29),(55,0.44),(65,0.67),(100,0.67
))
Units: dmnl
overall--0.23, in Rebeck et al., 2014 summary n small, not very
                    reliable

292

"Table Age vs D+ Sakr et al., 1994 Caucasian American"(
        [(0,0)-(100,1)],(25,0),(35,0.33),(45,0.36),(55,0.62),(65,0.6),(100,0.6))
Units: dmnl
overall--0.36, in Rebeck et al., 2014 summary-- overall 0.36

"Table Age vs D+ Sanchez-Chapado et al., 2003. Spain"(
        [(25,0)-(100,0.9)],(25,0.0358),(35,0.0882),(45,0.1428),(55,0.238),(65,0.317
),(75,0.333),(100,0.333))
Units: dmnl
29. Sanchez-Chapado M, Olmedilla G, Cabeza M, Donat E, Ruiz A.
                Prevalence of prostate cancer and prostatic intraepithelial
                neoplasia in Caucasian Mediterranean males: an autopsy study.
                Prostate. 2003;54(3):238-247. [PubMed]
                http://www.ncbi.nlm.nih.gov/pubmed/12518329 in Haas et al.,
                2008. The Worldwide Epidemiology of Prostate Cancer:
                Perspectives from Autopsy Studies
                http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2706483/ Table age
                groups 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90

"Table Age vs D+ Soos et al., 2005. Hungary"(
        [(25,0)-(100,1)],(25,0),(35,0.15),(45,0.266),(55,0.321),(65,0.5),(75,0.647
),(85,0.866),(100,1))
Units: dmnl
31. Soos G, Tsakiris I, Szanto J, Turzo C, Haas GP, Dezso B. The
                prevalence of prostate carcinoma and its precursor in Hungary:
                an autopsy study. Eur Urol. 2005;48(5):739-744. [PubMed] average
                38.8%, after 1994 autopsy study. in Rebbeck and Haas.
                http://www.ncbi.nlm.nih.gov/pubmed/16203079 N=139-- 0, 15, 26.6,
                32.1, 50, 64.7, 86.6, 86.6 for 90+--average 38.8 in: Haas et
                al., 2008. The Worldwide Epidemiology of Prostate Cancer:
                Perspectives from Autopsy Studies.
                http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2706483/ Table age
                groups 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90

"Table Age vs D+ Stamatiou, 2006. Greece"(
        [(25,0)-(95,1)],(25,0),(35,0),(45,0.026),(55,0.052),(65,0.138),(75,0.305),
(85,0.4),(95,0.562))
Units: dmnl
30. Stamatiou K, Alevizos A, Perimeni D, Sofras F, Agapitos E.
                Frequency of impalpable prostate adenocarcinoma and precancerous
                conditions in Greek male population: an autopsy study. Prostate
                Cancer Prostatic Dis. 2006;9(1):45-49. [PubMed]
                http://www.ncbi.nlm.nih.gov/pubmed/16314890 study conducted in
                2006. in: Haas et al., 2008. The Worldwide Epidemiology of
                Prostate Cancer: Perspectives from Autopsy Studies

"Table Age vs D+ Welch book"=
        1
Units: dmnl
Prostate Cancer Reservoir Found in Men after Accidental Death,
                Welch, Schwartz and Woloshin, 2011- Book page 48.

"Table Age vs D+ Yatani et al., 1988 Japan 1965-1979"(
        [(0,0)-(200,1)],(25,0),(55,0.1133),(65,0.2013),(75,0.2458),(85,0.404),(100
,0.404))
Units: dmnl
19. Yatani R, Shiraishi T, Nakakuki K, Kusano I, Takanari H,
                Hayashi T, Stemmermann GN. Trends in frequency of latent
                prostate carcinoma in Japan from 1965-1979 to 1982-1986. J Natl
                Cancer Inst. 1988;80(9):683-687. [PubMed]

http://www.ncbi.nlm.nih.gov/pubmed/3373558 Figure 1: Age
distribution of subjects found to have latent prostate carcinoma
postmortem. Table age groups 21-30, 31-40, 41-50, 51-60, 61-70,
71-80, 81-90 in: Haas et al., 2008. The Worldwide Epidemiology
of Prostate Cancer: Perspectives from Autopsy
Studies-http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2706483/

"Table Age vs D+ Yatani et al., 1988 Japan 1982-1986"(
        [(25,0)-(100,0.9)]],(25,0),(35,0.2),(45,0.13),(55,0.22),(65,0.35),(75,0.41)
,(85,0.48),(100,0.48))
Units: dmnl
19. Yatani R, Shiraishi T, Nakakuki K, Kusano I, Takanari H,
                Hayashi T, Stemmermann GN. Trends in frequency of latent
                prostate carcinoma in Japan from 1965-1979 to 1982-1986. J Natl
                Cancer Inst. 1988;80(9):683-687. [PubMed]
                http://www.ncbi.nlm.nih.gov/pubmed/3373558 Figure 1: Age
                distribution of subjects found to have latent prostate carcinoma
                postmortem. Table age groups 21-30, 31-40, 41-50, 51-60, 61-70,
                71-80, 81-90 in: Haas et al., 2008. The Worldwide Epidemiology
                of Prostate Cancer: Perspectives from Autopsy
                Studies-http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2706483/

"Table D+ for CDF Jacobsen 1996, 50-59"(
        [(0,0)-(100,100)],(0,0),(0.412421,5.49478),(1.42036,11.1563),(2.23094,17.1631
),(4.14617,27.9715),(4.4132,17.3162),(5.55227,34.145),(5.63423,28.1305),(7.45127
,39.2834),(7.73305,33.7826),(8.64084,39.1013),(8.65706,44.7713),(10.64,44.5825
),(10.6582,50.9397),(11.3514,50.5901),(11.4648,55.572),(14.739,56.0594),(14.8509
,60.5258),(20.406,60.9935),(20.8179,66.3165),(22.305,66.1319),(22.4219,72.3165
),(23.4278,77.2907),(23.8098,72.1328),(26.2066,77.9541),(26.4133,80.8734),(
29.6913,82.7352),(38.3197,82.8329),(38.5333,88.1576),(43.2101,93.6157),(60.5655
,93.6385),(1000,100))
Units: dmnl
Jacobsen et al. 1996- http://www.ncbi.nlm.nih.gov/pubmed/8944739
                This population-based case-control study was conducted in
                Olmsted County, Minnesota, where the Rochester Epidemiology
                Project could identify all incident cases of prostate cancer
                through passive surveillance of medical care provided to local
                residents. Case patients were all 177 men (age range, 50-79
                years) who were newly diagnosed as having prostate cancer from
                1990 through 1992 and had a prediagnostic serum PSA
                determination (90% of all incident cases). Control patients were
                randomly selected from the Olmsted County population and had
                undergone a clinical examination to exclude prostate cancer.

"Table D+ for CDF Jacobsen 1996, 60-79"(
        [(0,0)-(100,100)],(0,0),(1.30939,7.03348),(1.59952,4.45365),(2.41305,11.4914
),(3.23768,10.8543),(3.32117,16.9246),(4.776,17.0267),(4.8019,26.0758),(6.00769
,31.5637),(6.55201,36.9428),(7.67595,36.9332),(7.75846,42.6599),(8.75902,45.7441
),(8.9672,49.1788),(10.3016,53.4056),(10.4492,58.7881),(11.5797,61.0694),(12.5152
,64.4978),(12.9858,67.2429),(13.2562,69.3024),(16.0346,69.8513),(16.2402,72.3696
),(17.5003,73.7334),(18.5012,76.9321),(20.8878,79.2026),(21.7539,81.4861),(
24.2004,81.5797),(29.626,83.0222),(32.6084,85.5166),(38.161,85.1253),(38.4336
,87.9866),(43.1948,88.2894),(46.5038,89.4064),(56.2239,89.7811),(57.6843,91.8304
),(59.998,91.696),(1000,100))
Units: dmnl
Jacobsen et al. 1996- http://www.ncbi.nlm.nih.gov/pubmed/8944739
                This population-based case-control study was conducted in
                Olmsted County, Minnesota, where the Rochester Epidemiology
                Project could identify all incident cases of prostate cancer
                through passive surveillance of medical care provided to local
                residents. Case patients were all 177 men (age range, 50-79

years) who were newly diagnosed as having prostate cancer from
1990 through 1992 and had a prediagnostic serum PSA
determination (90% of all incident cases). Control patients were
randomly selected from the Olmsted County population and had
undergone a clinical examination to exclude prostate cancer.

"Table D+ for CDF Porter et al., 2006 men 60+"(
        [(0,0)-(25,1)],(0,0),(1,0.67),(2,0.74),(3,0.8),(4,0.85),(7,0.95),(10,0.98)
,(25,1),(100,1))
Units: dmnl

"Table D+ for CDF Zhang et al., 2012"(
        [(0,0)-(20,1)],(0,0),(1,0.138),(2.5,0.367),(4,0.559),(7,0.785),(10,0.888),
(50,0.999),(100,1))
Units: dmnl
PSA tests done in Olmsted County, Minnesota from 1983 to 2005.
                There are a total of 11,872 men underwent PSA testing during
                this timeframe with a total of 50,589 PSA test results --page 5.
                p at 50 value is missing.
                http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3288242/

"Table D- for CDF Jacobsen 1996, 50-59"(
        [(0,0)-(10,100)],(0,0),(0.45,30.2409),(0.679445,64.1413),(1.16191,71.01),(
1.84502,78.6789),(2.06139,84.9772),(3.75064,97.6776),(7.06027,99.0237),(9.50748
,99.3463),(12.2191,99.6667),(1000,100))
Units: dmnl
Jacobsen et al. 1996- http://www.ncbi.nlm.nih.gov/pubmed/8944739
                This population-based case-control study was conducted in
                Olmsted County, Minnesota, where the Rochester Epidemiology
                Project could identify all incident cases of prostate cancer
                through passive surveillance of medical care provided to local
                residents. Case patients were all 177 men (age range, 50-79
                years) who were newly diagnosed as having prostate cancer from
                1990 through 1992 and had a prediagnostic serum PSA
                determination (90% of all incident cases). Control patients were
                randomly selected from the Olmsted County population and had
                undergone a clinical examination to exclude prostate cancer.

"Table D- for CDF Jacobsen 1996, 60-69"(
        [(0,0)-(100,100)],(0,0),(0.645896,29.3188),(1.31895,56.5756),(3.10938,81.5317
),(3.9787,84.9607),(4.05891,89.8856),(4.79961,94.5757),(5.79591,96.1709),(6.19751
,97.8856),(7.39117,99.1354),(9.44136,99.3469),(1000,100))
Units: dmnl
Jacobsen et al. 1996- http://www.ncbi.nlm.nih.gov/pubmed/8944739
                This population-based case-control study was conducted in
                Olmsted County, Minnesota, where the Rochester Epidemiology
                Project could identify all incident cases of prostate cancer
                through passive surveillance of medical care provided to local
                residents. Case patients were all 177 men (age range, 50-79
                years) who were newly diagnosed as having prostate cancer from
                1990 through 1992 and had a prediagnostic serum PSA
                determination (90% of all incident cases). Control patients were
                randomly selected from the Olmsted County population and had
                undergone a clinical examination to exclude prostate cancer.

"Table D- for CDF Jacobsen 1996, 70-79"(
        [(0,0)-(80,100)],(0,0),(0.976794,29.4305),(1.12312,34.3549),(1.4632,37.6739
),(1.82557,48.7819),(2.12805,62.067),(3.36368,77.9786),(3.89947,80.3795),(4.70202
,83.5799),(5.1799,88.8451),(5.51932,91.935),(6.45246,94.5615),(7.51586,96.4997
),(8.24705,97.868),(9.8351,98.3126),(1000,100))
Units: dmnl

295

Jacobsen et al. 1996- http://www.ncbi.nlm.nih.gov/pubmed/8944739
This population-based case-control study was conducted in
Olmsted County, Minnesota, where the Rochester Epidemiology
Project could identify all incident cases of prostate cancer
through passive surveillance of medical care provided to local
residents. Case patients were all 177 men (age range, 50-79
years) who were newly diagnosed as having prostate cancer from
1990 through 1992 and had a prediagnostic serum PSA
determination (90% of all incident cases). Control patients were
randomly selected from the Olmsted County population and had
undergone a clinical examination to exclude prostate cancer.

"Table D- for CDF Porter et al., 2006 men 40-49"(
        [(0,0)-(20,100)],(0,0),(0.5,32.3),(1,73.3),(2,95.1),(3,97.8),(4,98.4),(100
,100))
Units: dmnl

"Table D- for CDF Porter et al., 2006 men 60-69"(
        [(0,0)-(20,100)],(0,0),(0.5,20.4),(1,50.2),(2,76.3),(3,87),(4,94.4),(100,100
))
Units: dmnl

"Table D- for CDF Porter et al., 2006 men 70-79"(
        [(0,0)-(10,100)],(0,0),(0.5,11.9),(1,33),(2,51.7),(3,65.8),(4,79),(12,100)
,(100,100))
Units: dmnl

"Table D- for CDF Zhang et al., 2012"(
        [(0,0)-(20,1)],(0,0),(1,0.471),(2.5,0.808),(4,0.909),(7,0.968),(10,0.983),
(50,1),(100,1))
Units: dmnl
PSA tests done in Olmsted County, Minnesota from 1983 to 2005.
        There are a total of 11,872 men underwent PSA testing during
        this timeframe with a total of 50,589 PSA test results --page 5.
        http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3288242/

Table Eff of T on Cost of Treatment(
        [(0,0)-(1,1.5)],(0,0.5),(0.25,0.8),(0.5,1),(0.75,1.2),(1,1.4))
Units: dmnl
is there any reference T in 1975? should there be a base or
        reference T? http://www.ncbi.nlm.nih.gov/books/NBK234309/
        Maximum technology is assumed to increase treatment costs by
        30%? check cost of treatment data oin excel sheet, should be
        about 40%

Table Eff of T on Harms(
        [(0,0)-(1,1)],(0,1),(0.117647,0.839858),(0.25,0.7),(0.362353,0.587189),(0.5
,0.5),(0.672941,0.412811),(0.832941,0.348754),(1,0.3))
Units: dmnl
this table is probably different for prostate and breast harm
        reduction techniques? or speed of progress in T is different

Table for Biopsy Detection(
        [(1980,0)-(2040,1)],(1980,0.64),(1990,0.7),(2000,0.75),(2010,0.8),(2020,1)
,(2030,1),(2040,1))
Units: dmnl
PCSIM PAGE 9. Etzioni et al., 2008- pg.
        326.http://www.ncbi.nlm.nih.gov/pubmed/18319508 Underwood et
        al., 2012- Table 3: http://www.ncbi.nlm.nih.gov/pubmed/22302420.
        Biopsy detection rate varied using 0.64 to 0.96. This is not to
        be confused with the harm reduction technology, T.

296

[(1980,0)-(2040,1)],(1980,0.64),(1990,0.7),(2000,0.75),(2010,0.8)
,(2020,1),(2030,1),(2040,1)
[(1980,0)-(2040,1)],(1980,0.53),(1985,0.53),(1990,0.8),(2000,0.96
),(2010,0.98),(2020,1),(2030,1),(2040,1):
http://www.ncbi.nlm.nih.gov/pubmed/20530126 pg. 711

Table for Biopsy Sensitivity(
        [(1985,0)-(2010,1)],(1970,0.55),(1986,0.55),(1990,0.8),(1995,0.8),(1997,0.82
),(2005,0.95),(2010,1),(2050,1))
Units: dmnl
page 19- 6 core sensitivity is 80% sensitive, 8+ cores are 100%
                sensitive, the proportion of 6-core scemens increase linearly
                after 1995 in favor of 8+ cores. biopsy sensitivity to be forced
                to 100% within n=2 years after transitioning to M1 metastatic
                disease.

"Table for CDF Vickers et al. 2010"(
        [(0,0)-(15,99)],(0,0),(0.43,10),(0.65,25),(1.06,50),(1.5,67),(1.92,75),(2.12
,80),(3.4,90),(5.17,95),(14.8,99),(50,99.9),(1000,100))
Units: dmnl
Centile vs PSA (ng/ml) from Vickers et al., 2010-- for age 60

"Table for Effect of Age on D+"(
        [(30,0)-(80,0.6)],(30,0.05),(40,0.15),(50,0.25),(60,0.35),(70,0.45),(80,0.55
))
Units: dmnl
REAL D+ is UNKNOWN, we use estimates coming from autopsy series.
                Prevalence is the number of cases of a particular condition that
                exists in a given population and consists of diagnosed cases
                plus those cases that are present but yet undetected. Prostate
                cancer prevalence can be estimated from a variety of sources.
                Several decades ago, many prostate cancers were discovered
                during the pathological examination of specimens from
                transurethreal prostatectomies. These patients were operated for
                suspected benign prostatic hyperplasia (BPH), but up to 25 per
                cent were found to have malignancy.5,6 Several authors
                investigated the prevalence of prostate cancer in
                cystoprostatectomy specimens, an operation usually carried out
                for the treatment of invasive bladder cancer. 25% to 40% of
                prostates were found to contain unsuspected prostate cancer.7-10
                (Haas et al., 2008)

Table for Empirical pdf(
        [(0,0)-(10,10)],(0,1),(1,1))
Units: dmnl
Centile vs PSA (ng/ml) from Vickers et al., 2010--IN EXCEL
                DIGITIZED DATA

Table Function for RandD(
        [(0,0)-(1,1)],(0,1),(1,1))
Units: dmnl

Table Practice Variation(
        [(-15,0)-(15,1)],(-15,0),(-10.4824,0.057),(-7.72941,0.117),(-5,0.224),(-2.5
,0.37),(0,0.5),(2.5,0.634),(5,0.776),(7.5,0.889),(10,0.972),(15,1))
Units: dmnl

"Table ROC for PSA Etzioni et al., 2004"(
        [(0,0)-(1,1)],(0,0),(0.0157,0.1363),(0.0283,0.1536),(0.033,0.18181),(0.05,
0.18861),(0.06089,0.2251),(0.065,0.2377),(0.069291,0.258621),(0.0745,0.26907
),(0.08,0.3),(0.086,0.3286),(0.091,0.334),(0.1144,0.3777),(0.127,0.4184),(0.145932

,0.4331),(0.165879,0.447753),(0.186877,0.4686),(0.207874,0.544932),(0.230971
,0.6013),(0.2561,0.644),(0.29186,0.67),(0.341207,0.7476),(0.464042,0.867816
),(0.5238,0.9242),(0.6845,0.9524),(0.86,0.964995),(1,1))
Units: dmnl
Etzioni et al., 2004:
　　　　　　　http://www.ncbi.nlm.nih.gov/pubmed/15466981 IS THIS EVERYBODY?
　　　　　　　WHAT IS AUC?

"Table ROC for PSA Jacobsen et al., 1996 age 50-59"(
　　　　[(0,0)-(1,1)],(0,0),(0.00186732,0.549412),(0.0110716,0.54945),(0.0132657,0.66469
),(0.0586649,0.829493),(0.0610873,0.884374),(0.22018,0.887773),(0.226558,0.939927
),(0.36836,0.995383),(0.98373,0.999287),(1,1))
Units: dmnl

"Table ROC for PSA Jacobsen et al., 1996 age 60-69"(
　　　　[(0,0)-(1,1)],(0,0),(0.0157,0.1363),(0.0283,0.1536),(0.033,0.18181),(0.05,
0.18861),(0.06089,0.2251),(0.065,0.2377),(0.069291,0.258621),(0.0745,0.26907
),(0.08,0.3),(0.086,0.3286),(0.091,0.334),(0.1144,0.3777),(0.127,0.4184),(0.145932
,0.4331),(0.165879,0.447753),(0.186877,0.4686),(0.207874,0.544932),(0.230971
,0.6013),(0.2561,0.644),(0.29186,0.67),(0.341207,0.7476),(0.464042,0.867816
),(0.5238,0.9242),(0.6845,0.9524),(0.86,0.964995),(1,1))
Units: dmnl

"Table ROC for PSA Jacobsen et al., 1996 age 70-79"(
　　　　[(0,0)-(1,1)],(0,0),(0.00564086,0.594697),(0.011908,0.502127),(0.0278853,0.623596
),(0.0293013,0.596852),(0.0460087,0.69912),(0.0476244,0.619562),(0.0813555,
0.740419),(0.0815059,0.700638),(0.114197,0.748785),(0.114223,0.741926),(0.157552
,0.758566),(0.157573,0.753079),(0.167973,0.784673),(0.170686,0.762736),(0.200586
,0.853397),(0.200841,0.78618),(0.209739,0.867153),(0.212436,0.849331),(0.22543
,0.890538),(0.225497,0.872705),(0.300369,0.89359),(0.333215,0.900584),(0.354192
,0.917132),(0.542135,0.941226),(0.543517,0.923398),(0.5934,0.945552),(0.681478
,0.951402),(0.691956,0.96242),(0.762904,0.977801),(0.762955,0.964084),(0.893095
,0.974222),(0.895621,1),(1,1))
Units: dmnl
jacobsen et al. 1996

"Table ROC for PSA Jacobsen et al., 1996 AUC=0.72"(
　　　　[(0,0)-(1,1)],(0,0),(0.0143666,0.069692),(0.0300489,0.13802),(0.0470402,0.210448
),(0.0798191,0.26787),(0.123107,0.328038),(0.149354,0.355397),(0.169006,0.401872
),(0.229399,0.444304),(0.253031,0.46073),(0.280566,0.508582),(0.312038,0.560538
),(0.348756,0.620697),(0.413067,0.682261),(0.480018,0.734265),(0.520716,0.764375
),(0.56403,0.804052),(0.604703,0.853288),(0.65063,0.905264),(0.716295,0.935408
),(0.778031,0.954618),(0.818746,0.971067),(0.877869,0.979345),(0.931738,0.984883
),(0.989545,0.994525),(1,1))
Units: dmnl
figure 3. jacobsen et al., 1996- panel C. AUC=0.72.

"Table ROC for PSA Jacobsen et al., 1996 AUC=0.83"(
　　　　[(0,0)-(1,1)],(0,0),(0.0152461,0.282504),(0.0248979,0.393864),(0.0444038,0.509368
),(0.10142,0.606392),(0.176304,0.641598),(0.221576,0.691176),(0.266878,0.724258
),(0.339716,0.798635),(0.426388,0.858607),(0.532807,0.906249),(0.641241,0.931215
),(0.74377,0.949983),(0.862089,0.962598),(0.962638,0.985486),(0.994169,0.999984
),(1,1))
Units: dmnl
figure 3. jacobsen et al., 1996- panel B. AUC=0.83. is this D+
　　　　　　　or overall population?

"Table ROC for PSA, Ahn et al. 2014 AUC=0.577"(
　　　　[(0,0)-(1,1)],(0,0),(0.0242482,0.0298266),(0.0797644,0.0526511),(0.11618,0.0771904
),(0.135187,0.129671),(0.17157,0.173442),(0.209635,0.248683),(0.232072,0.325646
),(0.273672,0.364181),(0.292691,0.409669),(0.327361,0.43945),(0.355109,0.456981

298

),(0.368913,0.505957),(0.407017,0.558471),(0.469424,0.612776),(0.521426,0.66007
),(0.556048,0.717823),(0.661842,0.780946),(0.776232,0.893035),(0.84215,0.924619
),(0.887222,0.963159),(0.965317,0.980778),(1,1))
Units: dmnl
ahn et al. 2014 auc=0.577

"Table ROC for PSA, Ferro et al., 2015"(
        [(0,0)-(1,1)],(0,0),(0.0208271,0.0217948),(0.0464358,0.0559562),(0.0639132
,0.11771),(0.098961,0.213526),(0.127744,0.260034),(0.170995,0.30672),(0.228643
,0.375122),(0.254376,0.372362),(0.27817,0.46804),(0.310158,0.517664),(0.346937
,0.576579),(0.396692,0.601807),(0.444787,0.642399),(0.483195,0.695179),(0.532908
,0.732714),(0.564864,0.791569),(0.651491,0.84802),(0.734944,0.892124),(0.813533
,0.948476),(0.909889,0.980431),(0.982171,0.999782),(1,1))
Units: dmnl
Ferro et al., 2015--AUC= 0.639 (0.592-0.687)

"Table ROC for PSA, Steuber et al., 2008"(
        [(0,0)-(1,1)],(0,0),(0.0108163,0.0553176),(0.0411861,0.0663138),(0.076929,
0.0911456),(0.0859723,0.190844),(0.132449,0.232267),(0.15043,0.34025),(0.20586
,0.403809),(0.243424,0.459107),(0.259553,0.508924),(0.284652,0.594727),(0.320417
,0.638949),(0.409724,0.658093),(0.440142,0.71064),(0.502702,0.763099),(0.568834
,0.815547),(0.613506,0.840354),(0.613506,0.840354),(0.713521,0.853928),(0.772523
,0.917476),(0.843996,0.95606),(0.927969,0.994608),(1,0.999965))
Units: dmnl
STEUBER ET AL., 2008

"Table ROC for PSA, Thompson et al., 2005 AUC=0.678"(
        [(0,0)-(1,1)],(0,0),(0.0229244,0.0658477),(0.040774,0.136822),(0.0636109,0.205233
),(0.10396,0.276094),(0.141771,0.339353),(0.176996,0.384858),(0.224782,0.442991
),(0.267606,0.508762),(0.325467,0.582072),(0.39579,0.647704),(0.471076,0.705696
),(0.551436,0.778892),(0.629234,0.83941),(0.812192,0.932388),(0.89734,0.962413
),(1,1))
Units: dmnl
Thompson et al., 2005. Empirical PSA curve: Operating
                Characteristics of Prostate-Specific Antigen in Men With an
                Initial PSA Level of 3.0 ng/mL or Lower. JAMA.
                2005;294(1):66-70. http://www.ncbi.nlm.nih.gov/pubmed/15998892
                Any PCa vs no PCa (AUC=0.678)

"Table ROC for PSA, Thompson et al., 2005 Gleason>7 or no PCa"(
        [(0,0)-(1,1)],(0,0),(0.0231494,0.111531),(0.0463238,0.248468),(0.0642109,0.327056
),(0.0995725,0.40048),(0.11996,0.479055
),(0.150284,0.54489),(0.200607,0.610624),(0.246006,0.691611),(0.328817,0.754641
),(0.406577,0.807545),(0.481888,0.870614)
,(0.599573,0.908087),(0.68472,0.938111),(0.722269,0.948073),(0.767268,0.947845
),(0.844916,0.977907),(0.90749,0.992818),(
1,1))
Units: dmnl
Thompson et al., 2005. Empirical PSA curve: Operating
                Characteristics of Prostate-Specific Antigen in Men With an
                Initial PSA Level of 3.0 ng/mL or Lower. JAMA.
                2005;294(1):66-70. http://www.ncbi.nlm.nih.gov/pubmed/15998892
                Gleason grade>=7 (high grade) vs. Gleason grade<7 (low grade) or
                No PCa (AUC=0.782)

"Table ROC for PSA, Thompson et al., 2005 Gleason>8 or no PCa"(
        [(0,0)-(1,1)],(0,0),(0.0107372,0.129361),(0.0290493,0.29424),(0.059561,0.398145
),(0.079923,0.471644),(0.11011,0.509562),(0.142796,0.547466),(0.168196,0.628555
),(0.20107,0.704529),(0.253994,0.790554),(0.271756,0.843762),(0.321742,0.840971
),(0.351854,0.86366),(0.406852,0.863381),(0.529762,0.946512),(0.669746,0.943264
),(0.854916,0.977856),(1,1))

Units: dmnl
Thompson et al., 2005. Empirical PSA curve: Operating
        Characteristics of Prostate-Specific Antigen in Men With an
        Initial PSA Level of 3.0 ng/mL or Lower. JAMA.
        2005;294(1):66-70. http://www.ncbi.nlm.nih.gov/pubmed/15998892
        Gleason grade>=8 vs. Gleason grade<8 or No PCa (AUC=0.827)

"Table ROC for PSA, Underwood et al. 2012"(
     [(0,0)-(1,1)],(0,0),(0.00745342,0.0697674),(0.0223602,0.132267),(0.0310559
,0.178779),(0.0434783,0.235465),(0.0559006,0.284884),(0.0770186,0.337209),(
0.0956522,0.375),(0.120497,0.422965),(0.146584,0.460756),(0.182609,0.497093
),(0.213665,0.52907),(0.270807,0.579942),(0.330435,0.62936),(0.386335,0.667151
),(0.453416,0.712209),(0.518012,0.752907),(0.573913,0.780523),(0.626087,0.806686
),(0.689441,0.838663),(0.73913,0.861919),(0.8,0.890988),(0.862112,0.917151)
,(0.893168,0.934593),(0.936646,0.954942),(0.971429,0.97093),(1,1))
Units: dmnl
Underwood et al., 2012--data from Zhang et al., 2012. Receiver
        Operating Characteristic (ROC) curve illustrating the imperfect
        nature of PSA testing based on longitudinal data for a regional
        population in Rochester, MN. 1983-2005, N=11.872 men, mean
        age=63, 95% Caucasian.
        http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3711512/
        http://www.ncbi.nlm.nih.gov/pubmed/21933990 We obtained the
        results of all PSA tests done in Olmsted County, Minnesota from
        1983 to 2005. There are a total of 11,872 men underwent PSA
        testing during this timeframe with a total of 50,589 PSA test
        results. The medical records linkage system of the Rochester
        Epidemiology Project (17) was then used to identify all patients
        that underwent a prostate biopsy or that had a pathologic
        diagnosis of prostate cancer during this same period of time.

Table Starting Age(
     [(-10,0)-(10,1)],(-10,0),(-7.5,0.05),(-5,0.1),(-2.5,0.25),(0,0.5),(2.5,0.75
),(5,0.9),(7.5,0.95),(10,1))
Units: dmnl
Table function representing the effect of starting age on screen
        eligible fraction.
        [(-10,0)-(10,1)],(-10,0),(-7.5,0.05),(-5,0.1),(-2.5,0.25),(0,0.5)
        ,(2.5,0.75),(5,0.9),(7.5,0.95),(10,1)

Table Starting Age to Screen(
     [(1980,0)-(2040,100)],(1980,100),(1985,50),(1990,40),(1995,40),(2000,45),(
2005,45),(2010,50),(2020,60),(2040,80))
Units: dmnl
endogeneous comes from the core model, thats the main reference
        behavior of the actual starting age over the years.

Table Stopping Age(
     [(-10,0)-(10,1)],(-10,1),(-7.5,0.95),(-5,0.9),(-2.5,0.75),(0,0.5),(2.5,0.25
),(5,0.1),(7.5,0.05),(10,0))
Units: dmnl
Table function representing the effect of stopping age on screen
        eligible fraction.
        [(-10,0)-(10,1)],(-10,1),(-7.5,0.95),(-5,0.9),(-2.5,0.75),(0,0.5)
        ,(2.5,0.25),(5,0.1),(7.5,0.05),(10,0)

Table T on Biopsy Detection(
     [(0,0)-(1,1)],(0,0),(0.25,0.6),(0.5,0.8),(0.75,0.9),(1,1))
Units: dmnl
Etzioni et al., 2008- pg.
        326.http://www.ncbi.nlm.nih.gov/pubmed/18319508 Underwood et

al., 2012- Table 3: http://www.ncbi.nlm.nih.gov/pubmed/22302420.
Biopsy detection rate varied using 0.64 to 0.96.

tdelta=
       0.01
Units: dmnl

Tech Funding dollars per year=
       1
Units: $/year

Technology T= INTEG (
       Innovation to Reduce Harms,
           Init Technology)
Units: dmnl
Harm Reduction Technology (T). Technology is the accumulation of
           the Innovation Rate (IR). Changes between 0-1. The innovation
           rate is computed as the product of the Innovation Fraction (IF),
           and Technology.

testoutcome:
       Tplus,Tminus

Threshold Switching[group]=
       IF THEN ELSE(Time>Screening Start Year, Switch T[group] , 0)
Units: dmnl
Switch is on if T is allowed to change endogeneously, off if set
           to be constant. 1986 is the year PSA screening has started. In
           signal detection theory, overall performance depends both on
           accuracy (otherwise known as 'sensitivity') of judgment and
           on the threshold (otherwise known as 'bias'). The standard
           measures of sensitivity and bias (e.g., Macmillan & Creelman,
           2005) assume normality, so they are not appropriate here.

Threshold T[group]= INTEG (
       Change in Threshold[group],
           INIT Threshold[group])
Units: dmnl
given in ng/ml. Threshold is the Cutoff value for the Test
           Outcome. Values above T will be considered as test positive
           (unhealthy), values below T will be considered as test negative
           (healthy). There is no specific normal or abnormal level of PSA
           in the blood. In the past, most doctors considered PSA levels of
           4.0 ng/mL and lower as normal. Therefore, if a man had a PSA
           level above 4.0 ng/mL, doctors would often recommend a prostate
           biopsy to determine whether prostate cancer was present.However,
           more recent studies have shown that some men with PSA levels
           below 4.0 ng/mL have prostate cancer and that many men with
           higher levels do not have prostate cancer (Thompson et al.,
           2004-NEJM-http://www.ncbi.nlm.nih.gov/pubmed/15163773). INFO
           SOURCE: http://www.cancer.gov/types/prostate/psa-fact-sheet

Threshold T2[group]= INTEG (
       Change in Threshold[group],
           INIT Threshold[group])
Units: dmnl
given in ng/ml. Threshold is the Cutoff value for the Test
           Outcome. Values above T will be considered as test positive
           (unhealthy), values below T will be considered as test negative
           (healthy). There is no specific normal or abnormal level of PSA
           in the blood. In the past, most doctors considered PSA levels of

301

4.0 ng/mL and lower as normal. Therefore, if a man had a PSA
level above 4.0 ng/mL, doctors would often recommend a prostate
biopsy to determine whether prostate cancer was present.However,
more recent studies have shown that some men with PSA levels
below 4.0 ng/mL have prostate cancer and that many men with
higher levels do not have prostate cancer (Thompson et al.,
2004-NEJM-http://www.ncbi.nlm.nih.gov/pubmed/15163773). INFO
SOURCE: http://www.cancer.gov/types/prostate/psa-fact-sheet

Threshold Table(
          [(1975,0)-(2050,10)],(1975,0),(1985,0),(1986,0),(1987,0),(1988,0),(1989,0)
,(1990,4),(1991,4),(1992,4),(1993,4),(1994,4),(1995,4),(1996,4),(1997,4),(1998
,4),(1999,4),(2000,4),(2001,4),(2002,4),(2003,4),(2004,4),(2005,4),(2006,0)
,(2050,0))
Units: dmnl
The standard for biopsy referral in the US from 1990 to 2005 was
          a PSA level greater than 4 ng/ml. Gulati et al., 2013. Their
          model allows men to get a biosy and diagnosis after screening if
          their PSA exceeds this threhold. Not realistic, in reality the
          de-facto (actual) PSA threshold used was 4 ng/ml or lower (up to
          2.5 ng/ml) in 1990's. Our model allows the formal and actual
          thresholds (or screening indications) to be different from each
          other, as the doctors, as well as the public, may not follow one
          set of recommendations.

ThrMaxDev=
          10
Units: dmnl

TIME STEP = 0.125
Units: year [0,?]
The time step for the simulation.

Time to Adj R[group]=
          2,2
Units: year
Time constant for change of recommended starting age

Time to Adj T[group]=
          2,2
Units: year
Adjustment time constant for the rate of change of the Threshold
                    value T.

Time to Cx=
          6
Units: year
Article: what if i dont treat my psa-detected prostate cancer?
          Mean years to Clinical detection (Cx)--lead time. Is it the SAME
          AS THE PREMETASTASIS CLINICAL DIAGNOSIS HAZARD??

TimeBtwSx=
          2
Units: year
Time between two consecutive screening tests. a diagnostic
          testing interval of 2 years is reasonably consistent with
          observed incidence. http://www.ncbi.nlm.nih.gov/pubmed/20530126
          pg. 713. 2

TimeToAct=
          0.5

Units: year
average time to proceed with the preferred treatment option.
                    time to reclassify= time to act-- time to start treatment
                    disease gets reclassified from M0 to M1, average time to
                    reclassify
                    http://www.theglobeandmail.com/life/health-and-fitness/health/mor
                    e-prostate-cancer-patients-being-monitored-instead-of-undergoing-
                    immediate-treatment-report/article28949464/

TimetoRecall=
        TimeBtwSx*relfollowup
Units: year
average time for a positive recall. follow up mean time is 3-4
                    months, or 6? find study to cite--add

Tmax=
        1
Units: dmnl

Total At Risk=
        SUM(Total At Risk by age[Age!])
Units: People

Total At Risk by age[Age]=
        At Risk Never Screened Pop[Age]+At Risk and Screened FP[Age]+At Risk and Screened TN
[Age]
Units: People

Total At Risk Never Screened=
        SUM(At Risk Never Screened Pop[Age!])
Units: People

Total At Risk Popn=
        SUM(Total At Risk Popn by age[Age!])
Units: People

Total At Risk Popn by age[Age]=
        At Risk Never Screened Pop[Age]+At Risk and Screened FP[Age]+At Risk and Screened TN
[Age]
Units: People

Total At Risk Screened FP=
        SUM(At Risk and Screened FP[Age!])
Units: People

Total At Risk Screened TN=
        SUM(At Risk and Screened TN[Age!])
Units: People

Total Cx M0=
        SUM(Cx LocoRegional M0[Age!,Grade!])
Units: People

Total Cx M1=
        SUM(Cx Distant M1[Age!,Grade!])
Units: People

Total CxM0=
        SUM(Tx CxM0[Age!,Grade!,Treatment!])
Units: People

Total CxM0M1=
        SUM(Tx CxM0M1[Age!,Grade!,Treatment!])
Units: People

Total CxM1=
        SUM(Tx CxM1[Age!,Grade!,Treatment!])
Units: People

Total death rate=
        XXocTotal+XXpcTotal
Units: People/year

Total Death Rate Per 100thou=
        Total Popn All Causes Death Rate*100000
Units: 1/year
total adult male popn death rate per 100.000 men

Total Deaths Time Series 1979to2014:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'F39')
Units: People/year
IS THIS 35++?

Total Diagnosed=
        SUM(Total Diagnosed by age grade[Age!,Grade!])
Units: People

Total Diagnosed by age grade[Age,Grade]=
        Cx LocoRegional M0[Age,Grade]+Sx LocoRegional M0[Age,Grade]+Sx Distant M1[
Age,Grade]+Cx Distant M1[Age,Grade]
Units: People
DIAGNOSED BUT NOT TREATED--YET. Cancer survivor: any person
                diagnosed with cancer, from the time of initial diagnosis until
                his or her death. Assuming constant incidence, survival, and
                cost, projection is 13.8 and 18.1 million cancer survivors in
                2010 and 2020, respectively, with associated costs of cancer
                care of 124.57 and 157.77 billion 2010 US dollars.
                http://jnci.oxfordjournals.org/content/103/2/117.long.
                http://costprojections.cancer.gov/cancer.prevalance.html

Total Dplus=
        Total M0+Total M1
Units: People

Total F=
        F1+F2+F3+F4+F5+F6
Units: dmnl

Total Indolent=
        Total M0 by grade[Latent]
Units: People

Total M0=
        SUM(Total M0 by grade[Grade!])
Units: People

Total M0 All Causes Death Rate=
        Total M0 OC Death Rate + Total M0 PCa Death Rate
Units: 1/year

Total M0 by age[Age]=
        SUM(Total M0 by age grade[Age,Grade!])

304

Units: People

Total M0 by age grade[Age,Grade]=
        Cx LocoRegional M0[Age,Grade]+Sx LocoRegional M0[Age,Grade]+Ux LocoRegional M0
[Age,Grade]+SUM(Tx CxM0[Age,Grade
        ,Treatment!])+SUM(Tx SxM0[Age,Grade,Treatment!])
Units: People

Total M0 by grade[Grade]=
        SUM(Total M0 by age grade[Age!,Grade])
Units: People

Total M0 OC Death Rate=
        ZIDZ(XXocM0Total,Total Popn M0)
Units: 1/year

Total M0 PCa Death Rate=
        XXpcM0Total/Total Popn M0
Units: 1/year

Total M1=
        SUM(Total M1 by grade[Grade!])
Units: People

Total M1 All Causes Death Rate=
        Total M1 OC Death Rate + Total M1 PCa Death Rate
Units: 1/year

Total M1 by age[Age]=
        SUM(Total M1 by age grade[Age,Grade!])
Units: People

Total M1 by age grade[Age,Grade]=
        Cx Distant M1[Age,Grade]+Sx Distant M1[Age,Grade]+Ux Distant M1[Age,Grade]
+SUM(Tx CxM0M1[Age,Grade,Treatment!])+SUM(Tx SxM0M1
        [Age,Grade,Treatment!])+SUM(Tx SxM1[Age,Grade,Treatment!])+SUM(Tx CxM1[Age
,Grade,Treatment!])
Units: People

Total M1 by grade[Grade]=
        SUM(Total M1 by age grade[Age!,Grade])
Units: People

Total M1 OC Death Rate=
        XXocM1Total/Total Popn M1
Units: 1/year

Total M1 PCa Death Rate=
        XXpcM1Total/Total Popn M1
Units: 1/year

Total Male Deaths Projected Time Series:INTERPOLATE::=
        GET XLS DATA('PSA.xlsx','Sheet1','2', 'AP29')
Units: People/year
Census, Table 15. NP2014-T5. Projected Components of Change by
                Race and Hispanic Origin for the United States: 2015 to 2060
                This gives all male+female. 0.492 male. then multiply with 35+
                death fraction of all deaths. The other thing you should do is
                to check your deaths against Vital Statistics historical deaths
                for each age group. Here are tables for 1999-2007:
                http://www.cdc.gov/nchs/nvss/mortality/gmwk310.htm

https://www.ssa.gov/oact/NOTES/as120/LifeTables_Tbl_1.html#wp1229
200, and for males:
https://www.ssa.gov/oact/NOTES/as120/LifeTables_Tbl_4a.html#wp100
5233
https://www.ssa.gov/oact/NOTES/as120/LifeTables_Tbl_4a.html#wp100
5233 projections till 2100

Total Popn=
	SUM(Total At Risk by age[Age!])+SUM(Total M0 by age grade[Age!,Grade!])+SUM
(Total M1 by age grade[Age!,Grade!])
Units: People

Total Popn above 50=
	SUM(Total Popn by age[Age50Plus!])
Units: People

Total Popn above 65=
	SUM(Total Popn by age[Age65Plus!])
Units: People

Total Popn above 65 cohorts[Age65Plus]=
	Total Popn by age[Age65Plus]
Units: People

Total Popn All Ages=
	Popn Below 35DATA+Total Popn
Units: People

Total Popn ALL Ages Historical:INTERPOLATE::=
	GET XLS DATA('PSA.xlsx','Sheet1','2', 'G129')
Units: People

Total Popn All Causes Death Rate=
	XXTotal/Total Popn
Units: 1/year

Total Popn below 50=
	SUM(Total Popn by age[AgeUnder50!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
		localized stage before the age of 65 years is associated with a
		specific survival of less than 30%.
		http://www.ncbi.nlm.nih.gov/pubmed/9410329

Total Popn below 65=
	SUM(Total Popn by age[AgeUnder65!])
Units: People
In the absence of curative treatment, a cancer diagnosed at the
		localized stage before the age of 65 years is associated with a
		specific survival of less than 30%.
		http://www.ncbi.nlm.nih.gov/pubmed/9410329

Total Popn below 65 cohorts[AgeUnder65]=
	Total Popn by age[AgeUnder65]
Units: People

Total Popn by age[Age]=
	Total At Risk by age[Age]+SUM(Total M0 by age grade[Age,Grade!])+SUM(Total M1 by age grade
[Age,Grade!])
Units: People

306

Total Popn Incidence Rate=
         Reported PCa Incidence/Total Popn
Units: 1/year

Total Popn M0=
         SUM(Total M0 by age grade[Age!,Grade!])
Units: People

Total Popn M1=
         SUM(Total M1 by age grade[Age!,Grade!])
Units: People

Total Popn OC Death Rate=
         XXocTotal/Total Popn
Units: 1/year

Total Popn PCa Death Rate=
         XXpcTotal/Total Popn
Units: 1/year

Total Popn Time Series 1979to2014:INTERPOLATE::=
         GET XLS DATA('PSA.xlsx','Sheet1','2', 'F47')
Units: People
http://wonder.cdc.gov/mortSQL.html group results by: gender, age
                  group, year--all male

Total Popn Time Series ALL AGES=
         Adult men popn counts 0to34+Total Popn Time Series 1979to2014
Units: People

Total Sx M0=
         SUM(Sx LocoRegional M0[Age!,Grade!])
Units: People

Total Sx M1=
         SUM(Sx Distant M1[Age!,Grade!])
Units: People

Total Tx=
         Total TxCx+Total TxSx
Units: People

Total TxCx=
         Total CxM0+Total CxM0M1+Total CxM1
Units: People

Total TxCx M0=
         SUM(Tx CxM0[Age!,Grade!,Treatment!])
Units: People

Total TxCx M1=
         SUM(Tx CxM1[Age!,Grade!,Treatment!])+SUM(Tx CxM0M1[Age!,Grade!,Treatment!]
)
Units: People

Total TxSx=
         Total TxSxM0+Total TxSxM0M1+Total TxSxM1
Units: People

Total TxSxM0=
         SUM(Tx SxM0[Age!,Grade!,Treatment!])

Units: People

Total TxSxM0M1=
        SUM(Tx SxM0M1[Age!,Grade!,Treatment!])
Units: People

Total TxSxM1=
        SUM(Tx SxM1[Age!,Grade!,Treatment!])
Units: People

Total Undiagnosed=
        SUM(Total Undiagnosed by age[Age!])
Units: People

Total Undiagnosed by age[Age]=
        SUM(Total Undiagnosed by age grade[Age,Grade!])
Units: People

Total Undiagnosed by age grade[Age,Grade]=
        Ux LocoRegional M0[Age,Grade]+Ux Distant M1[Age,Grade]
Units: People

Total Undiagnosed by grade[Grade]=
        SUM(Total Undiagnosed by age grade[Age!,Grade])
Units: People

Total Ux M0=
        SUM(Ux LocoRegional M0[Age!,Grade!])
Units: People

Total Ux M1=
        SUM(Ux Distant M1[Age!,Grade!])
Units: People

TP=
        1-"CDF of Threshold for D+"
Units: dmnl
True positive fraction

TplusAll=
        F1+F2+F3
Units: dmnl

Treated Total=
        SUM(Nr Treated by grade[Grade!])
Units: People

Treatment:
        ActiveSurveillance,RadioTheraphy,RadicalProstatectomy
AS= Active Surveillance= Watchful Waiting= Expectant Management=
                Conservative Management RT= Radiotherapy RP= Radical
                Prostatectomy

Treatment Distributions=
        1
Units: dmnl
Page 26. empirical distributions for treatment choices
                conservative management (CM-none), radical prostatectomy (RP),
                and radiation therapy (RT) provide treatment options among
                individuals diagnosed with local regional stage disease (M0), by
                grade at diagnosis (Gleason score 2-7 and Gleason 8-10).

308

Similary empirical proportions of men receiving Androgen
Deprivation Theraphy (ADT) are used by grade at diagnosis.

Treatment QALYs for localized PCa treatment=
        1
Units: dmnl
Litwin et al., 1995. JAMA. Quality-of-Life Outcomes in Men
        Treated for Localized Prostate Cancer.
        http://jama.jamanetwork.com/article.aspx?articleid=385793

"Treatment Rate (people/yr)"=
        1
Units: dmnl

Treatment Switch=
        1
Units: dmnl [0,1,0.5]

TreatmentFrom:
        ActiveSurveillance,RadioTheraphy,RadicalProstatectomy

TreatmentTo:
        ActiveSurveillance,RadioTheraphy,RadicalProstatectomy

True cases initial=
        1000
Units: People

"True Neg Rate (TNR)"[delta]=
        1-"False Pos Rate (FPR)"[delta]
Units: dmnl
True negative rate

"True Pos Rate (TPR)"[delta]=
        1-(NCDF((LnEffThreshold[delta]-"Mu D+")/(2*"Sigma D+")^0.5))
Units: dmnl
True positive rate, also known as the "True positive fraction".
        =P(T+/D+). TPR is defined as the fraction of correctly
        classified diseased subjects. In signal detection theory,
        overall performance depends both on accuracy (otherwise known as
        'sensitivity' or 'TPR') of judgment and on the threshold
        (otherwise known as 'bias'). 1-(NCDF((Effective
        Threshold-"Mean D+")/(2*"Stdev D+")^0.5))

Tx CxM0[Age,Grade,Treatment]= INTEG (
        EnterAgeTxCxM0[Age,Grade,Treatment]+txCxM0[Age,Grade,Treatment]-LeaveAgeTxCxM0
[Age,Grade,Treatment]-mxTxCxM0[Age,Grade,
        Treatment]-XXocTxCxM0[Age,Grade,Treatment]-XXpcTxCxM0[Age,Grade,Treatment]
+EnterTreatCxM0[Age,Grade,Treatment]-SUM(LeaveTreatCxM0
        [Age,Grade,Treatment,TreatmentTo!])+ImmTxCxM0[Age,Grade,Treatment],
        Adult men popn millions initial 1980[Age]*Init Fract Dplus[Age]*Init Fract M0
[Grade]*(1-Init Fract UxM0)*Init Fract DxTxM0*
        1/9*3*Init Grade[Grade])
Units: People
Clinically detected locoregional, low-grade cancer (M0G0)

Tx CxM0M1[Age,Grade,Treatment]= INTEG (
        EnterAgeTxCxM0M1[Age,Grade,Treatment]+EnterTreatCxM0M1[Age,Grade,Treatment
]+mxTxCxM0[Age,Grade,Treatment]-LeaveAgeTxCxM0M1
        [Age,Grade,Treatment]-SUM(LeaveTreatCxM0M1[Age,Grade,Treatment,TreatmentTo
!])-retxCxM1[Age,Grade,Treatment]-XXocTxCxM0M1

309

[Age,Grade,Treatment]-XXpcTxCxM0M1[Age,Grade,Treatment]+ImmTxCxM0M1[Age,Grade
,Treatment],
         Adult men popn millions initial 1980[Age]*Init Fract Dplus[Age]*(1-Init Fract M0
[Grade])*(1-Init Fract UxM1)*Init Fract DxTxM1
         *1/9*3*Init Grade[Grade])
Units: People
Treated for clinically detected M0, now M1 metastasized.
         Clinically detected distant-metastasized, low-grade cancer
         (M1G0). M1 corresponds to Clinical stage D, lymph node
         involvement or distant metastases. Represents distant cancer
         based on SEER.

Tx CxM1[Age,Grade,Treatment]= INTEG (
         EnterAgeTxCxM1[Age,Grade,Treatment]+retxCxM1[Age,Grade,Treatment]+txCxM1[Age
,Grade,Treatment]-LeaveAgeTxCxM1[Age,Grade,
         Treatment]-XXocTxCxM1[Age,Grade,Treatment]-XXpcTxCxM1[Age,Grade,Treatment]
+EnterTreatCxM1[Age,Grade,Treatment]-SUM(LeaveTreatCxM1
         [Age,Grade,Treatment,TreatmentTo!])+ImmTxCxM1[Age,Grade,Treatment],
             0)
Units: People
Treated for clinically detected M0, now M1 metastasized.
         Clinically detected distant-metastasized, low-grade cancer
         (M1G0). M1 corresponds to Clinical stage D, lymph node
         involvement or distant metastases. Represents distant cancer
         based on SEER.

Tx SxM0[Age,Grade,Treatment]= INTEG (
         EnterAgeTxSxM0[Age,Grade,Treatment]-LeaveAgeTxSxM0[Age,Grade,Treatment]+txSxM0
[Age,Grade,Treatment]-mxTxSxM0[Age,Grade,
         Treatment]-SUM(LeaveTreatSxM0[Age,Grade,Treatment,TreatmentTo!])+EnterTreatSxM0
[Age,Grade,Treatment]-XXocTxSxM0[Age,Grade
         ,Treatment]-XXpcTxSxM0[Age,Grade,Treatment]+ImmTxSxM0[Age,Grade,Treatment]

,
             0)
Units: People
Screen detected locoregional, low-grade cancer (M0G0). initial
         value is zero, no screening at the start of the simulation

Tx SxM0M1[Age,Grade,Treatment]= INTEG (
         EnterAgeTxSxM0M1[Age,Grade,Treatment]+EnterTreatSxM0M1[Age,Grade,Treatment
]+mxTxSxM0[Age,Grade,Treatment]-LeaveAgeTxSxM0M1
         [Age,Grade,Treatment]-SUM(LeaveTreatSxM0M1[Age,Grade,Treatment,TreatmentTo
!])-retxSxM1[Age,Grade,Treatment]-XXocTxSxM0M1
         [Age,Grade,Treatment]-XXpcTxSxM0M1[Age,Grade,Treatment]+ImmTxSxM0M1[Age,Grade
,Treatment],
             0)
Units: People
Treated for screen detected M0, now M1 metastasized. Screen
         detected distant-metastasized, low-grade cancer (M1G0). M1
         corresponds to Clinical stage D, lymph node involvement or
         distant metastases. Represents distant cancer based on SEER.
         initial value is zero, no screening at the start of the
         simulation

Tx SxM1[Age,Grade,Treatment]= INTEG (
         EnterAgeTxSxM1[Age,Grade,Treatment]+retxSxM1[Age,Grade,Treatment]+txSxM1[Age
,Grade,Treatment]-LeaveAgeTxSxM1[Age,Grade,
         Treatment]-XXocTxSxM1[Age,Grade,Treatment]-XXpcTxSxM1[Age,Grade,Treatment]
+EnterTreatSxM1[Age,Grade,Treatment]-SUM(LeaveTreatSxM1
         [Age,Grade,Treatment,TreatmentTo!])+ImmTxSxM1[Age,Grade,Treatment],
             0)

Units: People
Treated for screen detected M0, now M1 metastasized. Screen
detected distant-metastasized, low-grade cancer (M1G0). M1
corresponds to Clinical stage D, lymph node involvement or
distant metastases. Represents distant cancer based on
SEER.initial value is zero, no screening at the start of the
simulation

txCxM0[Age,Grade,Treatment]=
        Cx LocoRegional M0[Age,Grade]*pTxM0[Treatment]*Treatment Switch/TimeToAct
Units: People/year
treatment rate of clinically detected, Stage XX cancer

txCxM1[Age,Grade,Treatment]=
        Cx Distant M1[Age,Grade]*pTxM1[Treatment]*Treatment Switch/TimeToAct
Units: People/year
treatment rate of clinically detected, Stage XX cancer

TxM0[Age,Grade,Treatment]=
        Tx CxM0[Age,Grade,Treatment]+Tx SxM0[Age,Grade,Treatment]
Units: People

TxM1[Age,Grade,Treatment]=
        Tx SxM1[Age,Grade,Treatment]+Tx CxM1[Age,Grade,Treatment]+Tx SxM0M1[Age,Grade
,Treatment]+Tx CxM0M1[Age,Grade,Treatment]
Units: People

txRate by grade[Grade]=
        SUM(txRate by treatment grade[Grade,Treatment!])
Units: People/year

txRate by treatment[Treatment]=
        SUM(txRateM0[Age!,Grade!,Treatment])+SUM(txRateM1[Age!,Grade!,Treatment])
Units: People/year

txRate by treatment grade[Grade,Treatment]=
        txRateSx[Grade,Treatment]+txRateCx[Grade,Treatment]
Units: People/year

txRateCx[Grade,Treatment]=
        SUM(txRateCxPCa[Age!,Grade,Treatment])
Units: People/year

txRateCxPCa[Age,Grade,Treatment]=
        txCxM0[Age,Grade,Treatment]+txCxM1[Age,Grade,Treatment]
Units: People/year

txRateM0[Age,Grade,Treatment]=
        txCxM0[Age,Grade,Treatment]+txSxM0[Age,Grade,Treatment]
Units: People/year

txRateM1[Age,Grade,Treatment]=
        txCxM1[Age,Grade,Treatment]+txSxM1[Age,Grade,Treatment]
Units: People/year

txRateSx[Grade,Treatment]=
        SUM(txRateSxPCa[Age!,Grade,Treatment])
Units: People/year

txRateSxPCa[Age,Grade,Treatment]=
        txSxM0[Age,Grade,Treatment]+txSxM1[Age,Grade,Treatment]

311

Units: People/year

txSxM0[Age,Grade,Treatment]=
        Sx LocoRegional M0[Age,Grade]*pTxM0[Treatment]*Treatment Switch/TimeToAct
Units: People/year
treatment rate of screen detected, Stage XX cancer they ALL get
                some form of treatment.. active surveillance may be considered
                as minimum treatment after being detected.

txSxM1[Age,Grade,Treatment]=
        pTxM1[Treatment]*Sx Distant M1[Age,Grade]*Treatment Switch/TimeToAct
Units: People/year
treatment rate of screen detected, Stage XX cancer

Undiagnosed Deaths=0
Units: People/year

Unit Benefit[prof,testoutcome,diseasestate]=
        3,3,0;0,0,0.5;
Unit Benefit[advoc,testoutcome,diseasestate]=
                3,3,0;0,0,0.5;
        Units: dmnl
        Non-negative unit benefits for possible test outcome and disease
                        state pairs 3,0;0,0.5; 6,0;0,0.75;

Unit Cost[prof,testoutcome,diseasestate]=
        0,0,1.5;2,2,0;
Unit Cost[advoc,testoutcome,diseasestate]=
                0,0,1.5;2,2,0;
        Units: dmnl
        non-negative unit costs for possible test outcome and disease
                        state pairs 0,1.5;2,0; 0,0.5;1,0;
                        UtilityDplusTplus2,UtilityDzeroTplus2,UtilityDminusTplus2;Utility
                        DplusTminus2,UtilityDzeroTminus2,UtilityDminusTminus2;

Unnecessary Biopsy Rate by age[Age]=
        People with Unnecessary Biopsies Per Year[Age]*Number of Biopsies Per FP Case
Units: Biopsies/year

UtilityDminusTminus=
        0
Units: dmnl

UtilityDminusTminus2=
        0
Units: dmnl

UtilityDminusTplus=
        Instantaneous Biopsy Disutility*BiopCompM0
Units: dmnl
INSTANTNEOUS BIOPSY DISUTILITY TIMES BIOPSY COMPLIANCE.
                simplification: i used the complioance for M0 disease, it is
                higher for M1

UtilityDminusTplus2=
        UtilityDminusTplus*Effect of HRT on Harms
Units: dmnl
biopsy disutility goes down with HRT

UtilityDplusTminus=
        Disutility Due to Cancer Death*PrCancerDeathWithoutScreen

312

Units: dmnl

UtilityDplusTminus2=
        UtilityDplusTminus
Units: dmnl

UtilityDplusTplus=
        Disutility Due to Treatment+Disutility Due to Cancer Death*PrCancerDeathWithScreen
Units: dmnl

UtilityDplusTplus2=
        Disutility Due to Treatment*Effect of HRT on Harms+Disutility Due to Cancer Death
*PrCancerDeathWithScreen
Units: dmnl

UtilityDzeroTminus=
        0
Units: dmnl

UtilityDzeroTminus2=
        0
Units: dmnl

UtilityDzeroTplus=
        Disutility Due to Treatment
Units: dmnl

UtilityDzeroTplus2=
        UtilityDzeroTplus*Effect of HRT on Harms
Units: dmnl
disutility of treatment of indolent disease goes down with HRT

Ux Distant M1[Age,Grade]= INTEG (
        EnterAgeUxM1[Age,Grade]+ImmUxM1[Age,Grade]+mxM0[Age,Grade]-cxM1[Age,Grade]
-LeaveAgeUxM1[Age,Grade]-sxM1[Age,Grade]-XXocUxM1[Age,Grade]-XXpcUxM1[Age,Grade
],
                Adult men popn millions initial 1980[Age]*Init Fract Dplus[Age]*(1-Init Fract M0
[Grade])*Init Fract UxM1*1/3*3*Init Grade[Grade])
Units: People
Undiagnosed, distant-metastasized cancer (M1). M1 corresponds to
                Clinical stage D, lymph node involvement or distant metastases.
                Represents distant cancer based on SEER. Advanced cancers
                include T3 tumors as extending beyond the prostate without
                positive scans or evidence of metastasis and T4 tumors defined
                as having at least 1 positive scan, positive lymph node, or
                distant metastasis (Hoffman et al., 2003). Staging guidelines
                used by SEER categorize all organ-confined tumors as stage B
                (Fleming Cooper and Henson et al., AJCC Cancer Staging Manual,
                1997).

Ux LocoRegional M0[Age,Grade]= INTEG (
        AsxInci[Age,Grade]+AsxInci2[Age,Grade]+AsxInci3[Age,Grade]+EnterAgeUxM0[Age
,Grade]+ImmUxM0[Age,Grade]-cxM0[Age,Grade]-LeaveAgeUxM0[Age,Grade]-mxM0[Age
,Grade]-sxM0[Age,Grade]-XXocUxM0[Age,Grade]-XXpcUxM0[Age,Grade],
                Adult men popn millions initial 1980[Age]*Init Fract Dplus[Age]*Init Fract M0
[Grade]*1/3*Init Fract UxM0*3*Init Grade[Grade])
Units: People
Undiagnosed, Loco-regional cancer (M0) Grade and age specific.
                Low Grade=Gleason score 2-7, High Grade=Gleason Score 8-10.
                Indolent (nonprogressive)
Ux M0 High=0

Units: People
Clinical stage A, Clinically localized and nonpalpable on DRE.
                Represents local (stage I) cancer based on SEER. Clinically
                localized cancers include T1 and T2 tumors.
Ux M0 Ind=0
Units: People
Tumor is yet impalpable. Represents local (stages I) cancer
                based on SEER, that is of non-progressive type. NOTE: SEER
                doesnt make the distinction between progressive and
                non-progressive.
                chromeextension://oemmndcbldboiebfnladdacbdfmadadm/http://seer.ca
                ncer.gov/archive/manuals/historic/comp_stage1.1.pdf
Ux M1 High=0
Units: People
linical stage B, Clinically localized but palpable on DRE.
                Represents local (stage II) cancer based on SEER. T1 tumors are
                defined as confined to the prostate with a normal DRE and no
                positive scans, or evidence of metastasis. T2 tumors are defined
                as comfined to the prostate with abnormal or suspicious DRE's,
                but no positive scans or evidence of metastasis. (Hoffman et
                al., 2003).
UxM0[Age,Grade]=Ux LocoRegional M0[Age,Grade]
Units: People

UxM1[Age,Grade]=Ux Distant M1[Age,Grade]
Units: People
weight=0.5
Units: dmnl
Weighted Disutility EB=F1component+F2component+F3component+F4component+F5component+F6component
Units: dmnl
F1*UtilityDminusTplus2+F2*UtilityDzeroTplus2+F3*UtilityDplusTplus
                2+F4*UtilityDminusTminus2+F5*UtilityDzeroTminus2+F6*UtilityDplusT
                minus2
Weighted Disutility layperson=F11component+F22component+F33component+F44component
Units: dmnl
F11*UtilityDminusTplus2+F22*UtilityDplusTplus2+F33*UtilityDminusT
                minus2+F44*UtilityDplusTminus2
XXoc Per 100thou=XXocTotal/Total Popn*100000
Units: 1/year
XXocAtRisk[Age]=At Risk Never Screened Pop[Age]*dfAll[Age]
Units: People/year
Other cause (or all cause) mortality rate is indicated as XXoc.
XXocAtRisk Total=SUM(XXocTotalAtRisk by Age[Age!])
Units: People/year
XXocAtRiskFP[Age]=At Risk and Screened FP[Age]*dfAll[Age]
Units: People/year
XXocAtRiskTN[Age]=At Risk and Screened TN[Age]*dfAll[Age]
Units: People/year
XXocbyAge[Age]=XXocTotalAtRisk by Age[Age]+XXocDplusbyAge[Age]
Units: People/year
XXocCxM0[Age,Grade]=Cx LocoRegional M0[Age,Grade]*dfAll[Age]
Units: People/year
XXocCxM1[Age,Grade]=Cx Distant M1[Age,Grade]*dfAll[Age]
Units: People/year
XXocCxPCa by age grade[Age,Grade]=XXocCxM0[Age,Grade]+XXocCxM1[Age,Grade]
Units: People/year
XXocDistant[Age,Grade]=XXocUxM1[Age,Grade]+XXocCxM1[Age,Grade]+XXocSxM1[Age,Grade]+SUM(XXocTxCxM0M1
[Age,Grade,Treatment!])+SUM(XXocTxSxM0M1[Age
        ,Grade,Treatment!])+SUM(XXocTxSxM1[Age,Grade,Treatment!])+SUM(XXocTxCxM1[Age
,Grade,Treatment!])
Units: People/year

XXocDplusbyAge[Age]=SUM(XXocDistant[Age,Grade!])+SUM(XXocLocoReg[Age,Grade!])
Units: People/year
XXocDplusTotal=SUM(XXocDplusbyAge[Age!])
Units: People/year
XXocLocoReg[Age,Grade]=XXocUxM0[Age,Grade]+XXocCxM0[Age,Grade]+XXocSxM0[Age,Grade]+SUM(XXocTxCxM0
[Age,Grade,Treatment!])+SUM(XXocTxSxM0[Age,Grade,Treatment!])
Units: People/year
XXocM0Total=SUM(XXocLocoReg[Age!,Grade!])
Units: People/year
XXocM1AttributedtoPCa[Age,Grade]=XXocDistant[Age,Grade]*Attribution Bias
Units: People/year
XXocM1Total=SUM(XXocDistant[Age!,Grade!])
Units: People/year
XXocSxM0[Age,Grade]=Sx LocoRegional M0[Age,Grade]*dfAll[Age]
Units: People/year
XXocSxM1[Age,Grade]=Sx Distant M1[Age,Grade]*dfAll[Age]
Units: People/year
XXocSxPCa=SUM(XXocSxPCa by age grade[Age!,Grade!])
Units: People/year
XXocSxPCa by age grade[Age,Grade]=XXocSxM0[Age,Grade]+XXocSxM1[Age,Grade]
Units: People/year
XXocTotal=XXocAtRisk Total+XXocDplusTotal
Units: People/year
Real other cause death rate, per year
XXocTotalAtRisk by Age[Age]=XXocAtRisk[Age]+XXocAtRiskFP[Age]+XXocAtRiskTN[Age]
Units: People/year
XXocTxCxM0[Age,Grade,Treatment]=Tx CxM0[Age,Grade,Treatment]*dfAll[Age]
Units: People/year
XXocTxCxM0M1[Age,Grade,Treatment]=Tx CxM0M1[Age,Grade,Treatment]*dfAll[Age]
Units: People/year
XXocTxCxM1[Age,Grade,Treatment]=Tx CxM1[Age,Grade,Treatment]*dfAll[Age]
Units: People/year

XXocTxSxM0[Age,Grade,Treatment]=Tx SxM0[Age,Grade,Treatment]*dfAll[Age]
Units: People/year
XXocTxSxM0M1[Age,Grade,Treatment]=Tx SxM0M1[Age,Grade,Treatment]*dfAll[Age]
Units: People/year
XXocTxSxM1[Age,Grade,Treatment]=Tx SxM1[Age,Grade,Treatment]*dfAll[Age]
Units: People/year
XXocUxM0[Age,Grade]=Ux LocoRegional M0[Age,Grade]*dfAll[Age]
Units: People/year
XXocUxM1[Age,Grade]=Ux Distant M1[Age,Grade]*dfAll[Age]
Units: People/year
XXoxCxPCa=SUM(XXocCxPCa by age grade[Age!,Grade!])
Units: People/year
XXpc by age[Age]=XXpcM0 by age[Age]+XXpcM1 by age[Age]
Units: People/year
XXpcbyAge[Age]=SUM(XXpcM1 by age grade[Age,Grade!])+SUM(XXpcM0 by age grade[Age,Grade!])
Units: People/year
Real PCa death rate, per year
XXpcCxM0[Age,Grade]=Cx LocoRegional M0[Age,Grade]*dfM0[Grade]*PCaXXSwitch
Units: People/year
Prostate cancer (PCa) mortality rate is indicated as XXpc.
XXpcCxM1[Age,Grade]=Cx Distant M1[Age,Grade]*dfM1[Grade]*PCaXXSwitch
Units: People/year
Prostate cancer (PCa) mortality rate is indicated as XXpc.
XXpcEstimatedM0[Age,Grade]=XXpcCxM0[Age,Grade]+XXpcSxM0[Age,Grade]+SUM(XXpcTxCxM0[Age,Grade,Treatment
!])+SUM(XXpcTxSxM0[Age,Grade,Treatment!])+(XXpcUxM0[Age,Grade]*Fraction of undiagnosed disease discovered at
time of death)
Units: People/year

XXpcEstimatedM1[Age,Grade]=XXpcCxM1[Age,Grade]+XXpcSxM1[Age,Grade]+SUM(XXpcTxCxM0M1[Age,Grade,Treatment!])+SUM(XXpcTxSxM0M1[Age,Grade,Treatment!])+(XXpcUxM1[Age,Grade]*Fraction of undiagnosed disease discovered at time of death)
Units: People/year
XXpcEstimatedTotal=SUM(XXpcEstimatedM1[Age!,Grade!])+SUM(XXpcEstimatedM0[Age!,Grade!])+SUM(XXocM1Attribut
edtoPCa
[Age!,Grade!])
Units: People/year
XXpcM0=SUM(XXpcM0 by grade[Grade!])
Units: People/year

XXpcM0 by age[Age]=SUM(XXpcM0 by age grade[Age,Grade!])
Units: People/year
XXpcM0 by age
grade[Age,Grade]=XXpcCxM0[Age,Grade]+XXpcSxM0[Age,Grade]+XXpcUxM0[Age,Grade]+SUM(XXpcTxCxM0
[Age,Grade,Treatment!])+SUM(XXpcTxSxM0[Age,Grade,Treatment!])
Units: People/year
XXpcCxM0[Grade]+XXpcSxM0[Grade]+XXpcUxM0[Grade]+XXpcTxCxM0[Grade,
                  Treatment]+XXpcTxSxM0[Grade,Treatment]
XXpcM0 by grade[Grade]=
        SUM(XXpcM0 by age grade[Age!,Grade])
Units: People/year

XXpcM0Total=
        SUM(XXpcM0 by age grade[Age!,Grade!])
Units: People/year
XXpcM1=SUM(XXpcM1 by grade[Grade!])
Units: People/year
XXpcM1 by age[Age]=SUM(XXpcM1 by age grade[Age,Grade!])
Units: People/year
XXpcM1 by age grade[Age,Grade]=
        XXpcUxM1[Age,Grade]+XXpcCxM1[Age,Grade]+XXpcSxM1[Age,Grade]+SUM(XXpcTxCxM0M1
[Age,Grade,Treatment!])+SUM(XXpcTxSxM0M1[Age,Grade,Treatment!])
        +SUM(XXpcTxSxM1[Age,Grade,Treatment!])+SUM(XXpcTxCxM1[Age,Grade,Treatment!])
Units: People/year
XXpcM1 by grade[Grade]=SUM(XXpcM1 by age grade[Age!,Grade])
Units: People/year
XXpcM1Total=SUM(XXpcM1 by age grade[Age!,Grade!])
Units: People/year
XXpcSxM0[Age,Grade]=Sx LocoRegional M0[Age,Grade]*dfM0[Grade]*PCaXXSwitch
Units: People/year
Prostate cancer (PCa) mortality rate for Loco-regional,
                  low-grade cancer (M0G0)
XXpcSxM1[Age,Grade]=Sx Distant M1[Age,Grade]*dfM1[Grade]*PCaXXSwitch
Units: People/year
Prostate cancer (PCa) mortality rate is indicated as XXpc.
XXpcTotal=SUM(XXpcbyAge[Age!])
Units: People/year
XXpcTxCxM0[Age,Grade,Treatment]=Tx CxM0[Age,Grade,Treatment]*dfTxM0[Grade,Treatment]*PCaXXSwitch
Units: People/year
Prostate cancer (PCa) mortality rate is indicated as XXpc.
XXpcTxCxM0M1[Age,Grade,Treatment]=Tx CxM0M1[Age,Grade,Treatment]*dfM1TxM0[Grade,Treatment]*PCaXXSwitch
Units: People/year
Prostate cancer (PCa) mortality rate is indicated as XXpc.
XXpcTxCxM1[Age,Grade,Treatment]=Tx CxM1[Age,Grade,Treatment]*dfTxM1[Grade,Treatment]*PCaXXSwitch
Units: People/year
Prostate cancer (PCa) mortality rate is indicated as XXpc.
XXpcTxDistant[Grade,Treatment]=SUM(XXpcTxSxM0M1[Age!,Grade,Treatment])+SUM(XXpcTxCxM0M1[Age!,Grade,Trea
tment])+SUM(XXpcTxCxM1[Age!,Grade,Treatment])+SUM(XXpcTxSxM1[Age!,Grade,Treatment])
Units: People/year

XXpcTxLocoReg[Grade,Treatment]=SUM(XXpcTxCxM0[Age!,Grade,Treatment])+SUM(XXpcTxSxM0[Age!,Grade,Treatment])

Units: People/year

XXpcTxSxM0[Age,Grade,Treatment]=Tx SxM0[Age,Grade,Treatment]*dfTxM0[Grade,Treatment]*PCaXXSwitch

Units: People/year

Prostate cancer (PCa) mortality rate is indicated as XXpc.

XXpcTxSxM0M1[Age,Grade,Treatment]=Tx SxM0M1[Age,Grade,Treatment]*dfM1TxM0[Grade,Treatment]*PCaXXSwitch

Units: People/year

Prostate cancer (PCa) mortality rate is indicated as XXpc.

XXpcTxSxM1[Age,Grade,Treatment]=Tx SxM1[Age,Grade,Treatment]*dfTxM1[Grade,Treatment]*PCaXXSwitch

Units: People/year

Prostate cancer (PCa) mortality rate is indicated as XXpc.

XXpcUxM0[Age,Grade]=Ux LocoRegional M0[Age,Grade]*dfM0[Grade]*PCaXXSwitch

Units: People/year

Prostate cancer (PCa) mortality rate is indicated as XXpc.

XXpcUxM1[Age,Grade]=Ux Distant M1[Age,Grade]*dfM1[Grade]*PCaXXSwitch

Units: People/year

Prostate cancer (PCa) mortality rate is indicated as XXpc.

XXTotal=XXocTotal+XXpcTotal

Units: People/year

total death rate per year

XXtotal35to44=SUM(XXTotalbyAge[AgeGroup35to44!])

Units: People/year

XXtotal45to54=SUM(XXTotalbyAge[AgeGroup45to54!])

Units: People/year

XXtotal55to64=SUM(XXTotalbyAge[AgeGroup55to64!])

Units: People/year

XXtotal65plus=SUM(XXTotalbyAge[Age65Plus!])

Units: People/year

XXtotal65to74=SUM(XXTotalbyAge[AgeGroup65to74!])

Units: People/year

XXtotal75plus=SUM(XXTotalbyAge[AgeGroup75plus!])

Units: People/year

XXTotalAllAges=XXTotal+XXTotalbelow35

Units: People/year

IF THEN ELSE(Time<2010,XXTotal+XXTotalbelow35 , 0)

XXTotalAllAgesDATA:=GET XLS DATA('PSA.xlsx','Sheet1','2', 'F102')

Units: People/year

XXTotalbelow35:=GET XLS DATA('PSA.xlsx','Sheet1','2', 'F94')

Units: People/year

XXTotalbyAge[Age]=XXocbyAge[Age]+XXpcbyAge[Age]

Units: People/year

XXTotalDplus=SUM(XXocDplusbyAge[Age!])+SUM(XXpcbyAge[Age!])

Units: People/year

XXUndiagnosed=SUM(XXUndiagnosed by age[Age!])

Units: People/year

people who died without getting a diagnosis of PCa, healthy and diseased

XXUndiagnosed by age[Age]=XXUndiagnosedDminus by age[Age]+XXUndiagnosedDplus by age[Age]

Units: People/year

XXUndiagnosedDminus by age[Age]=XXocTotalAtRisk by Age[Age]

Units: People/year

XXUndiagnosedDplus by
age[Age]=SUM(XXocUxM0[Age,Grade!]+XXocUxM1[Age,Grade!]+XXpcUxM0[Age,Grade!]+XXpcUxM1[Age,Grade!])

Units: People/year

Yearly hazard of metastasis=0.1

Units: 1/year

yearly hazard of metastasis in different preclinical stages

(wever et al, 2009) paper has 9 parameers based on clinical
stage: T1, T2, T3, pathologic grade: G6, G7, G8, and Metastasis:

317

M0 for locoregional and M1 for distant. T2 total is 0.0637, T3
total is 0.1767
Years Per Cohort=Mean Cohort Size*Rate of Leaving Adult Age Category
Units: year
Cohort length, the number of years per cohort (YPC), or the average residence time before exiting via maturation. BD. section 12.1

Appendix R. Essay #2 Sensitivity Parameters

```
Fig 12.
HBR Trans Delay = 20
HBR Trans Delay = 16
HBR Trans Delay = 13
HBR Trans Delay = 10
HBR Trans Delay = 6
HBR Trans Delay = 3
HBR Trans Delay = 1


Fig 13.
HBR Multiplier = 0.1
HBR Multiplier = 0.2
HBR Multiplier = 0.3
HBR Multiplier = 0.4
HBR Multiplier = 0.5
HBR Multiplier = 0.7


Fig 14.

"Mu D-" = 1
"Sigma D-" = 0.6


Fig 15.

200,M,1234,,0
HBR Trans Delay=RANDOM_UNIFORM(2,15)
Public Perception Delay=RANDOM_UNIFORM(0.5,5)

Fig 16.

200,M,1234,,0
"% D+"=RANDOM_UNIFORM(0.05,0.5)

Fig 17.

200,M,1234,,0
"% D+"=RANDOM_UNIFORM(0.0,1.0)
```

Appendix S. Essay #3 Sensitivity Parameters

Fig 13.
Screen Switch = 0

Fig 27.

HBR Trans Delay = 6
HBR Trans Delay = 5
HBR Trans Delay = 4
HBR Trans Delay = 3

Fig 28.
Max Adoption Fraction = 0
Max Adoption Fraction = 0.25
Max Adoption Fraction = 0.5
Max Adoption Fraction = 1

Fig 31.
200,M,1234,,0
Biopsy Compliance Rate=RANDOM_UNIFORM(0.3,0.7)
Instantaneous Biopsy Disutility=RANDOM_UNIFORM(0.01,0.1)
Disutility End of Life=RANDOM_UNIFORM(0.15,1)
Annual Utility Decrement of Living With Treatment before
Metastasis=RANDOM_UNIFORM(0.05,0.24)

Fig 32-33.

200,M,1234,,0
Biopsy Compliance Rate=RANDOM_UNIFORM(0,0.7)
HBR Trans Delay=RANDOM_UNIFORM(2,10)
Max Adoption Fraction=RANDOM_UNIFORM(0.25,0.75)