The Economic and Ethical Considerations and Implications of the Stratification of Future Oncology Therapeutics

By

Sameer A. Sabir

M.B.A

Massachusetts Institute of Technology, 2008

B.Sc (Hons) Immunology, University College London, 2000

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Signature of Author:.....

Harvard-MIT Division of Health Sciences and Technology
And MIT Sloan School of Management, August 2009

Certified by:.....

Ernst R. Berndt, PhD
Louis E. Seely Professor in Applied Economics, MIT Sloan School of Management
Thesis Supervisor

Certified by:.....

Mark Trusheim
Visiting Scholar, MIT Sloan School of Management
Thesis Supervisor

Accepted by:.....

Ram Sasiekharan
Edward Hood Taplin Professor of Biological Engineering and Health Sciences and Technology
Director of Harvard-MIT Division of Health Sciences and Technology

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Submitted to the Harvard-MIT Division of Health Sciences and Technology in partial fulfillment of the requirements for the degree of Master of Science in Health Sciences and Technology

This thesis investigates the economic impact of stratified medicine on industry and the subsequent ethical implications for patients. Stratified medicine involves the use of clinical biomarkers to indicate differential response among patients in efficacy or potential side effects of therapeutic agents. The advent of stratified medicine should, in theory, result in the safer, more effective use of therapeutic agents to treat cancer. However, reluctance remains within the broader life sciences community, in particular within the pharmaceutical industry, to embrace stratified medicine. I hypothesize that this is due to economic concerns.

Firstly, an historical analysis of the rate of market adoption of stratified therapeutics is conducted by comparing the adoption velocity and time to peak sales of stratified therapeutics relative to traditional chemotherapeutics. The aim is to analyze whether historically, stratified medicines have been more or less successful in terms of speed of market adoption. To supplement this analysis interviews are conducted with investment analysts who cover pharmaceutical and diagnostics companies to gauge their views on stratified medicine. This is important due to the fact that publicly traded companies have an obligation to their shareholders, and shareholder views are shaped by the analyses of these individuals.

In order to assess the future economic impact of stratified medicine on industry, particularly given that clinical biomarkers are now being developed much earlier in the R&D timeline, a model was constructed to predict economic outcomes based on various parameters associated with biomarker development. The aim of this model is to investigate how factors such as pricing, drug efficacy and biomarker accuracy, amongst other factors, impact the patient population, and therefore market size and economic performance for a drug with an associated biomarker.

This body of analysis is then used to conduct a second set of interviews with representatives from patient advocacy groups to gauge their opinions on the ethical implications arising out of the economic considerations discussed in the first half of this thesis.

In summary, this thesis undertakes a comprehensive review of the history of the adoption of stratified medicine within oncological therapeutics, and a forward-looking analysis of the economic and ethical implications with the aim of clarifying the circumstances in which stratification may be appropriate. In doing so, this thesis provides a resource to pharmaceutical companies and patient advocates attempting to chart a viable path forward in this rapidly changing field.

Acknowledgements

This thesis is the culmination of three years of study in the Harvard-MIT Biomedical Enterprise Program. Through a curriculum consisting of business, management, basic medical science and clinical experience, I have experienced a learning opportunity that is entirely without parallel. To me, the highlight of this experience has been the opportunity to interact with a cohort of incredibly gifted, progressive and open-minded students who share the common aim of improving the lives of others through a shared interest in life sciences and healthcare. For the wonderful camaraderie and memories, I thank my fellow BEPers, particularly from the '09 and '10 class: Brian Miller, Brian Newkirk, Julie Yoo, Michael Magnani, Adam Weinstein, Will Crawford and Linsdsay Johnston. The other side of this equation is the BEP and MIT faculty, a fantastic group of individuals who are truly motivated to provide the best education possible to their charges, and also just happen to be leaders in their respective fields. Particular thanks go to Rox Anderson, Teo Dagi, Richard Cohen, Rick Mitchell, Shiv Pilai, Ken Morse and Carl Berke.

I owe a deep debt of gratitude to Professor Ernie Berndt, not just for his exceptional guidance and patience as my thesis supervisor, but also for his mentorship, support and friendship throughout the BEP experience. He is a true asset to MIT and to the BEP program and I hope to keep his acquaintance for many years to come.

This thesis attempts to tackle an issue that is becoming central to the delivery of healthcare in the oncology field and a focus of study in both academia and industry. I could not have achieved a fraction of what is in this thesis without the help and steadying hands of my thesis supervisors Ernie Berndt and Mark Trusheim. I would also like to thank individuals at the MIT Center for Biomedical Innovation (CBI), including Gigi Hirsch, Eli Lilly & Company for generously providing IMS data, and the investment analysts and representatives of patient advocacy groups that so patiently submitted themselves to my interviews. Thanks also to the other members of the 'Stratified Medicine Team' including Brian Newkirk and Lindsay Johnson.

Finally, I thank my wife Nada for her enduring patience and encouragement over the three years of this program, my parents for the sacrifices they made to get me to where I am, and my friends for keeping me sane.

Author's Biography

Sameer Sabir is a Master's candidate in the Harvard-MIT Biomedical Enterprise Program. He will receive his Master of Health Sciences and Technology from MIT in September 2009 and earned his M.B.A in June 2008 from the MIT Sloan School of Management. Prior to grauate school, Sameer worked for Cinnabar Consulting, a boutique business development and corporate finance company that he co-founded, focused on helping Scandinavian life sciences companies achieve their goals. Prior to Cinnabar Consulting, Sameer worked in life sciences investment banking, with JPMorgan and then Commerzbank Securities. Sameer holds a B.Sc (Hons) from University College London (UCL). During his M.B.A program, Sameer interned at Genentech Inc, in San Francisco. Upon graduation, Sameer will focus on MoMelan Technologies, a dermatology start-up he has co-founded with technology out of the Wellman Center for Photomedicine at MGH.

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1.Introduction

Cancer therapeutics have come a long way since the advent of chemotherapy in 1942 when nitrogen mustard was successfully administered to a patient with non-hodgkins lyphoma at Yale Cancer Center[1]. Since then, our understanding of tumor biology, regulatory pathways and cellular mechanisms has led to further advances in chemotherapy, radiotherapy and immunotherapy. Although these modes of treatment generally still form the mainstay of an oncologist's practice[2], novel insights have inevitably led to innovation in the drug discovery space, with a focus on more targeted therapeutics that selectively attack cancer cells[3].

Thus we now observe on the market drugs associated with clinical biomarkers. Tests are used to establish whether a patient expresses a gene for the relevant marker, indicating that the drug is likely to be effective or less likely to generate adverse events. Most drugs in this category are biotherapeutics (antibodies)[4] as opposed to traditional small molecules, and are considered by many to be the first generation of stratified, or personalized therapeutics.

Many of the first generation stratified therapeutics were not developed with this express intention. Indeed traditional clinical trials of these drugs initially appeared unsuccessful, with positive outcomes only in a subset of patients. Further investigation revealed commonality amongst the patients in terms of molecular markers, thus leading to a drug and associated biomarker. Blockbusters including Herceptin[5] (Genentech) owe their existence to these circumstances.

Outcomes that were initially the result of accidental discoveries are now the focus of intense research and development efforts within the life-sciences industry. Genentech, for example, has become one of the most successful biotechnology companies in history[6] through its biologics and biomarker-based approach, targeting large and lucrative indications such as non-hodgkin's lymphoma, breast cancer and lung cancer.

Yet reluctance remains within the broader life sciences community, and in particular large pharma[7], to embrace fully the concept of stratified medicine. Part of this may be the perception that stratified medicine is so strongly tied in connotation to genetics and the interpretation of the human genome, but I hypothesize that the resistance emanates mainly from an economic perspective[7].

My view is that stratification of medicine is the ability of a clinically relevant biomarker to measure the likelihood that a drug will work (diagnostic) or how well a drug is working (prognostic). This could be something as simple as using cholesterol levels as a marker for statin effectiveness. In oncology, a number of molecular biomarkers are proving to be progressively more important[8] from both a diagnostic and prognostic perspective.

The purpose of this thesis is to ask and then examine whether the traditional fears that concern big pharma are in fact valid. As a complement to this, I will examine potential scenarios based around the views of leading investment professionals and patient advocacy groups, along with both their economic and ethical implications.

Specifically, this thesis considers the following issues:

(1) **Challenges surrounding the market adoption of stratified oncology therapies.** A common fear from many within commercial organizations of large pharma appears to be that, due to the well-established treatment paradigms in many oncology indications, stratified medicines will initially be used reluctantly[9] and therefore take longer to achieve peak market share than their non-stratified comparables. This will in turn affect profitability, effective patent life and ultimately the bottom line. Using historical sales data for 'gold-standard' chemotherapeutics and comparing to stratified medicines, I aim, through statistical methods to establish whether stratified medicines generally take more, less or equivalent time to reach peak sales.

(2) **What are the views of investment professionals on stratified medicine?** Clearly many of the decisions surrounding R&D are taken with a commercial viewpoint, and these decisions are often driven by opinions on the street and ultimately shareholders[10]. Therefore through interviews both with Wall Street analysts and various large-pharma and life sciences executives I examine their views surrounding the future of stratified oncology therapeutics.

(3) **Scenarios – the future of stratified oncology therapeutics.** Using information from the first part of this research, I aim, through an in-house developed modeling tool, to examine the implications both of drug efficacy and biomarker efficacy on the commercial and ethical aspects of developing

and marketing a stratified oncology therapeutic. This will be done through consideration of various scenarios, adjusting both the efficacy of the drug as well as the sensitivity of the biomarker, to examine the resultant patient populations, potential market adoption and commercial outcomes.

(4) **Ethical implication of stratified oncology therapeutics.** Using information from the scenarios created in part (3), I will examine the ethical implications of decisions that may be taken on the basis of commercial merit, through interviews with patient advocacy groups, regarding the ethical implications of biomarker accuracy. Specifically, I will examine the importance of the specificity of biomarkers and the subsequent number of 'false positive responders' to examine how patients are affected who are not eligible for treatment but are included, and the relationship to commercial potential.

2.Historical Analysis – Chemotherapy vs Stratified Drugs

Many of the concerns surrounding stratified therapeutics have centered around the economic implications, such as a potential end to the blockbuster era. This line of reasoning hinges around two issues:

Firstly, there is a prevailing argument that a stratified therapeutic will reduce the overall market size of a particular indication, therefore reducing the potential for 'blockbuster,' or billion dollar sales. To some extent this is true. Any given drug is only effective in a certain percentage of the population who have the disease being treated, yet it is sold to all patients, regardless of whether it is effective for the individual. However, it has become increasingly clear that what is important and can compensate for loss of size of market is market penetration. Higher market penetration, combined with attracting new patients and better compliance within a smaller market, can result in a similar level of profitability. Drugs such as Rituxan and Herceptin have demonstrated this, both selling well in excess of $1bn per year[3].

Consequently, I hypothesize that what may be more relevant is the *rate* of market adoption. A significant concern within oncology is that gold-standard chemotherapeutics are so well-established and (relatively speaking) effective that oncologists will view new therapeutics with suspicion, thus preventing rapid adoption. This has an echo effect in terms of length of patent life and number of years at peak sales, and therefore profitability.

I set out to establish whether stratified medications do in fact take longer to achieve market adoption than do the traditional drugs used in oncology. In order to do this, I compare IMS data on US sales for gold-standard chemotherapeutics to data on US sales for stratified oncology drugs. In this analysis I set the launch date of each drug as time '0' and then examine reported sales data on a quarterly basis to assess time taken to reach peak unit volumes and adoption rates through a new measure, adoption velocity (described below).

The following topics will be covered in the remainder of this chapter:

- Description of drugs -An overview of the stratified and non-stratified therapeutics used in my analysis
- An analysis of the difference in adoption rates between stratified and non-stratified therapeutics based on 'adoption velocity' and time to peak unit volumes
- A discussion of the results and their implications

2.2 Description of Drugs

Drug	Type	Target	Mechanism
Gemzar	Non-stratified	NA	Folate anti-metabolites
Alimta	Non-Stratified	NA	Nucleoside analog
Taxotere	Non-Stratified	NA	Mitotic inhibitor
Erbitux	Stratified	EGFR	EGFR Inhibitor
Herceptin	Stratified	Her2/neu	Cell growth inhibition
Rituxan	Stratified	CD20	B-cell destruction
Arimidex	Stratified	Aromatase	Antihormonal
Femara	Stratified	Aromatase	Antihormonal
Gleevec	Stratified	Bcr-ABL/c-kit	Tyrosine kinase inhibitor
Tarceva	Stratified	EGFR	Tyrosine kinase inhibitor
Avastin	Stratified	VEGF-A	Angiogenesis inhibitor
Velcade	Stratified	26S proteosome	Proteosome inhibitor

Table 1: Drugs used in analysis

Traditional chemotherapeutics (non-stratified)

Medicines identified as traditional (non-stratified) chemotherapeutics have been chosen as they were, when launched, considered to be the 'gold standard' for chemotherapy and were thus readily embraced by oncologists. These drugs include:

Docetaxel (Taxotere) – An antimitotic therapy marketed by Sanofi Aventis, Taxotere is indicated for advanced, metastatic and non-small cell lung cancer, as well as some forms of breast and ovarian cancer. It is administered intravenously and is generally given every three weeks over a 10-dose cycle[11,12]. It generates approximately $2bn globally. Taxotere was first approved in the US in 1996 and is expected to lose patent protection in 2010.

Gemcitabine (Gemzar) – Gemzar is a nucleoside analogue marketed by Eli Lilly and Company and is currently indicated for pancreatic, breast, bladder and non-small cell lung cancer. It is given as an infusion, both standalone and in combination with carboplatin (for lung cancer)[13]. Gemzar dosing varies widely by indication. For example, it is used with carboplatin for lung cancer and administered three times during a 21 day cycle, with 4-6 cycles completing a course of treatment.[43] The cost of Gemzar is approximately $12,600 per course of treatment[44]. Gemzar was first approved in 1996 and is expected to lose patent protection in 2010.

Pemetrexed (Alimta) – Alimta is a folate antimetabolite marketed by Eli Lilly and Co. It is indicated for the treatment of malignant pleural mesothelioma and non-small-cell lung cancer[14]. It is administered intravenously, usually with cisplatin over a 21 day cycle as appropriate to the patient. It costs approximately

$3900/month[45].It was approved by the FDA in 2004, and is expected to lose patent protection in 2015.

Stratified Cancer Therapeutics

The drugs in this section are considered to be the 'first generation' of stratified oncology therapeutics. Each drug is associated with some form of diagnostic (or prognostic) biomarker:

Cetuximab (Erbitux) - Erbitux is an anti - Epidermal Growth Factor Receptor (EGF-R) monoclonal antibody indicated for the treatment of metastatic colorectal and 'head and neck' cancer[15]. It is administered intravenously ($30,000/ 8 weeks)[16]. It is marketed by Bristol Myers Squibb, was first approved by the FDA in 2006, and is expected to lose patent protection in 2017.

Bevacizumab (Avastin) - Avastin is an angiogensis inhibitor, an anti Vascular Endothelial Growth Factor - A (VEGF-A) monoclonal antibody indicated for the treatment of metastatic colon, non-small cell lung, and breast cancer, in combination with chemotherapy[17]. It is administered intravenously ($50,000/per year)[18]. It is marketed by Genentech/Roche, was first approved by the FDA in 2004, and is expected to lose patent protection in 2017.

Erlotinib (Tarceva) - Tarceva is a small-molecule drug, which targets the EGF-R Tyrosine Kinase (particularly JAK2V617F). It is indicated for refractory non-small cell lung cancer and advanced or inoperable pancreatic cancer[19]. It is marketed by Genentech/Roche and OSI Pharmaceuticals. Tarceva is a once a day (tablet or

capsule, not a pill) often used in combination with Gemzar ($90/day). Tarceva was first approved by the FDA in 2004 and is expected to lose patent protection in 2018.

Imatinib (Gleevec) – Gleevec is a small molecule tyrosine kinase inhibtor which acts selectively on *bcr-abl,* as well as c-kit and PDGF-A. It is indicated in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumours (GIST)[20] and is taken orally on a chronic basis ($37,000/year)[21]. It is marketed by Novartis, was first approved by the FDA in 2001, and is expected to lose patent protection in 2015.

Letrozole (Femara) – Femara is an aromatase inhibitor indicated for local or metastatic breast cancers that are hormone-receptor positive. Femara is taken orally once a day ($200/month). Femara is marketed by Novartis, was first approved by the FDA in 1997 (approved as a first line treatment for hormone positive breast cancer in 2001), and is expected to lose patent protection in 2011.[22]

Anastrozole (Arimidex) – Arimidex is an aromatase inhibitor indicated for post surgery and metastatic breast cancer in patients who are estrogen receptor positive.[23] Arimidex is taken once a day ($100/month), it is marketed by AstraZeneca, was first approved by the FDA in 2002, and is expected to lose patent protection in 2010.

Rituximab (Rituxan) – Rituxan is an anti CD20 (B-cell) chimeric monoclonal antibody indicated in the use of B-cell non-hodgkins lymphomas and leukemias. [24] It is now the standard of care in these cancers. Rituxan is administered weekly intravenously ($20,000/patient/year). It is marketed by Genentech (and Biogen

Idec), was first approved by the FDA in 1997, and is expected to lose patent protection in 2015.

Trastuzumab (Herceptin) – Herceptin is an anti Her2/Neu humanized monoclonal antibody indicated in the use of breast cancer where Her2/Neu is overexpressed[25] (although recent studies demonstrate it may also be effective in other breast cancers)[26]. Herceptin is administered intravenously weekly ($70,000/year).[27] Herceptin is marketed by Genentech. It was first approved by the FDA in 1998 and is expected to lose patent protection in 2019

Bortezamib (Velcade) – Velcade is a proteasome inhibitor indicated for the treatment of multiple myeloma and mantle cell lymphoma.[28] Protein M is used as a prognostic biomarker to measure Velcade efficacy. Velcade is administered intravenously over a 21 day cycle ($45,000/year).[46] Velcade is marketed by Millenium Pharmaceuticals, was first approved by the FDA in 2003, and is expected to lose patent protection in 2014.

2.3 Analysis

Methods

My data set consists of US sales data from IMS generously provided through Eli Lilly and Company. In order to eliminate variables related to pricing, currency fluctuations and general inflation I based my analysis on the number of standard unit sales over time, expressed as volume, charted on a quarterly basis.

Standard unit sales are defined by IMS MIDAS as the dosing unit delivered to the patient, and varies by packaging.[47]

Definition of terms

In order to conduct an effective analysis, I have broken the therapeutic data down into four categories:

1. Non-stratified (Mature)
2. Non-Stratified (New)
3. Stratified (Mature)
4. Stratified (New)

where mature indicates that a drug has been on the market for more than five years, and new for five years or less.

Definition of measures of analysis

Two primary measures are used in this analysis, and each is defined below:

Time to peak unit volume

'Time to peak unit volume' is a chronological measure expressed in years and indicates when a drug reaches 'peak unit volume sales.' It is calculated by observing the peak unit volume of a drug, which is the maximum observed unit volume, and the corresponding time taken in years to reach this point.

Using the example of Rituxan below where standard unit volume is charted against time, it can be seen that the peak unit volume of 478 standard units is reached in 8.5 years, as indicated by the vertical bar.

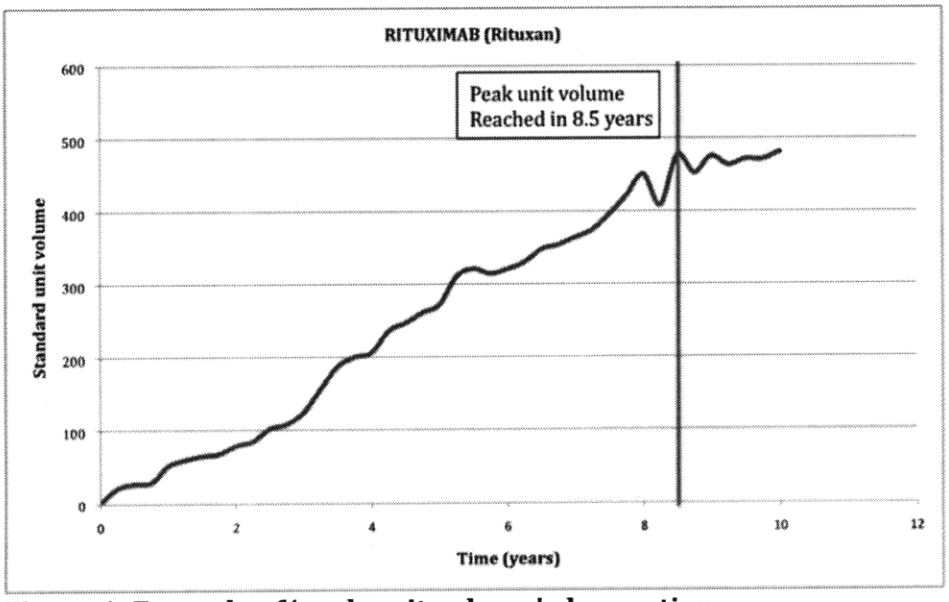

Figure 1: Example of 'peak unit volume' observation

Peak unit volume is a measure only applicable to 'mature drugs' as 'new drugs' have not yet reached peak unit volume.

Adoption Velocity

As part of my analysis I developed an analytical measure which has been named 'adoption velocity.' Adoption velocity is defined as the rate per year at which the peak normalized standard unit sales (volume) change over the defined time period. It is calculated as follows:

(1) The data for each drug is normalized to itself, using maximum observed unit volume in the defined time period as the denominator.

(2) A linear trendline with the equation y=mx+b is calculated, where:

a. y is the growth rate per quarter up to the quarter where peak unit volume is observed;

b. x is the number of years from launch (a calendar quarter is 0.25 year, as in Figure 2 below);

c. b is the y intercept, which is *not* forced to be 'zero';

d. m is the gradient of the slope and the 'adoption velocity'.

This is demonstrated below using Gemzar as an example. Figure 2 shows the standard unit sales (volume) of Gemzar for the first four years of sales.

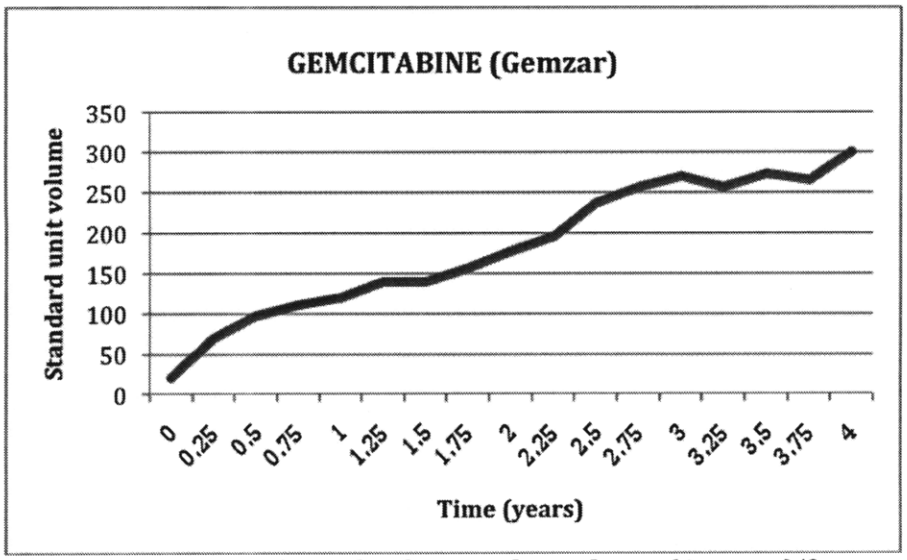

Figure 2: Example of standard unit sales volume (Gemzar)[42]

Figure 3 plots the normalized standard unit sales (volume) to the peak value observed over the time period. A linear trend line is then calculated whose slope is the adoption velocity using least squares regression techniques. The line is not forced to have a zero intercept[47].

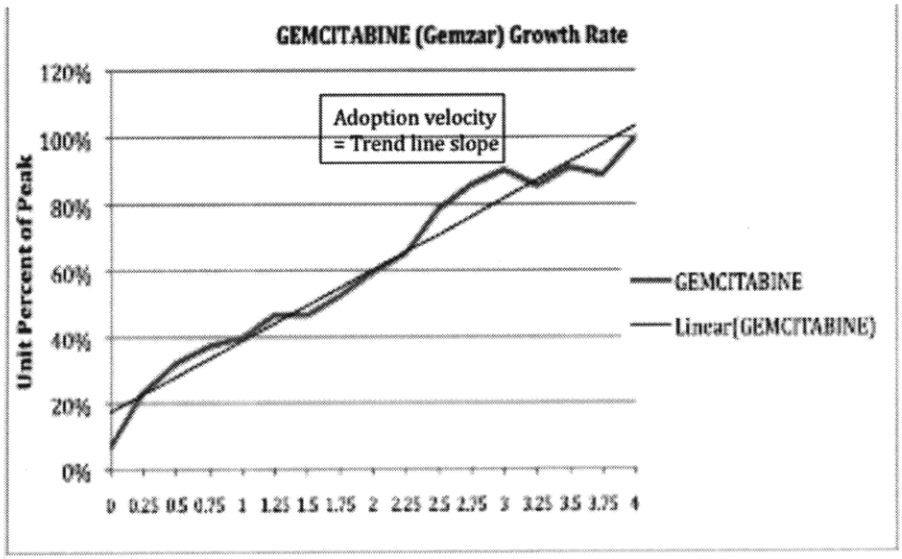

Figure 3: Example of adoption velocity calculation (Gemzar) [42]

The difference between 'adoption velocity' and 'traditional growth rates'

The adoption velocity measure is not a growth rate. It is based on data where the drug is normalized to itself as described, and in the linear regression calculation, the line is not forced to have a zero intercept. This has the advantage over a traditional growth rate as it corrects for the explosive growth and volatility in the first few quarters of sales and makes all drugs used in this analysis comparable to one another. A traditional growth rate would not correct for the explosive growth rate in the first few quarters and may make a 'like for like' comparison of different drugs difficult.'

The disadvantage of this measure is that it is highly sensitive to the number of time periods and becomes less meaningful particularly in cases where there is a long 'tail' or plateauing of unit volumes.

Classifications of adoption velocity

- 1- (New Drugs) – 'Over the lifetime' refers to the adoption velocity from time point '0' to the last quarterly reported sales data point;
- 2- (Mature Drugs) – '0-4 years' – refers to the adoption velocity for the first four years from time '0' to time '4 years';
- 3 -(Mature Drugs) – 'Over the lifetime' refers to the adoption velocity from time point '0' to peak unit volume as defined by the maximum observed standard unit volume.

It is important to note that classification 1 – 'new drugs over the lifetime' is comparable to classification 2 - 'mature drugs 0-4 years' for the purposes of analysis, but these two classifications are not comparable to classification 3 – 'mature drugs over the lifetime.'

Non Stratified Medicines

I consider taxotere and Gemzar to be 'mature' drugs, and Alimta to be a 'new drug'.

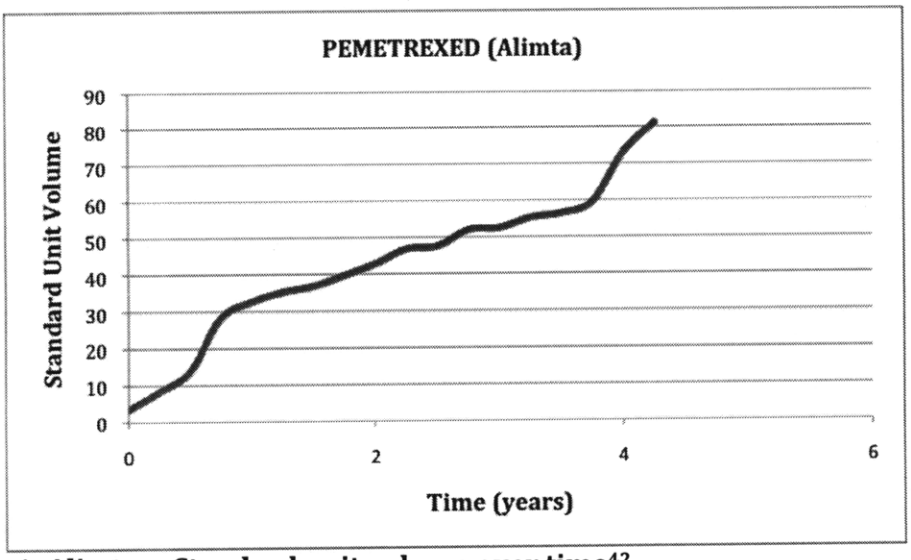

Figure 4: Alimta – Standard unit volume over time[42]

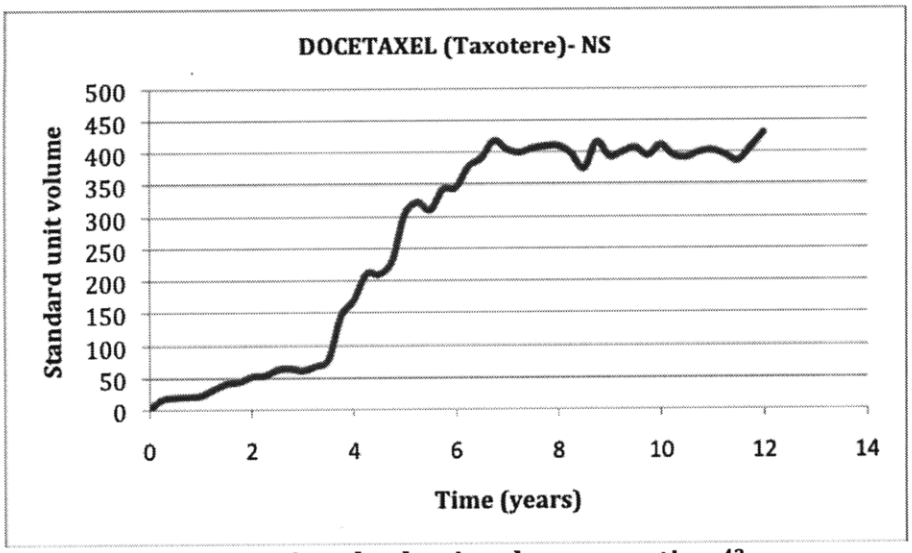

Figure 5: Taxotere – Standard unit volume over time[42]

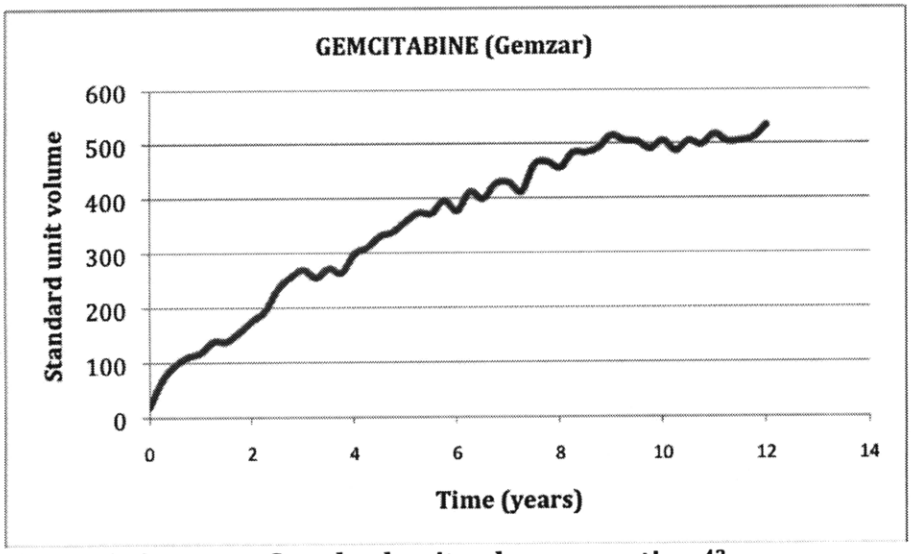

Figure 6: Gemzar – Standard unit volume over time[42]

The adoption velocity of Alimta over its lifetime is 20%. The adoption velocities of Gemzar and Taxotere from 0-4 years are 22% and 18% respectively (mean 20%, SD 2%). This indicates that the average growth profile of a chemotherapeutic drug is similar today to the profile of drugs launched 16-18 years ago. The adoption velocities of both Taxotere and Gemzar over their lifetime are 12% and 7% respectively (mean 10%, SD 3%).

It is interesting to note that after its first approval for advanced breast cancer in 1996,[29] the adoption velocity of Taxotere was 5% until it was approved for second-line treatment of non-small cell lung cancer (NSCLC) approximately four years later[30]. At this point adoption velocity increased to 12% until it reached peak unit volume. Subsequently the drug was also approved for first-line therapy in NSCLC[31] and gained several subsequent approvals for a variety of cancers. It can therefore truly be considered a 'gold standard' in terms of cancer therapeutics.

With regards to time to peak unit volume, Gemzar took nine years to reach peak unit volume. Taxotere took 8.75 years. Its growth rate accelerated after the second approval for NSCLC and from this point, 3.5-4 years after launch, took 5.25 years to reach peak unit volume.

Stratified Medicines

I consider Gleevec, Femara, Arimidex, Ritxuan and Herceptin to be mature stratified drugs, and Erbitux, Avastin, Tarceva and Velcade to be new stratified drugs.

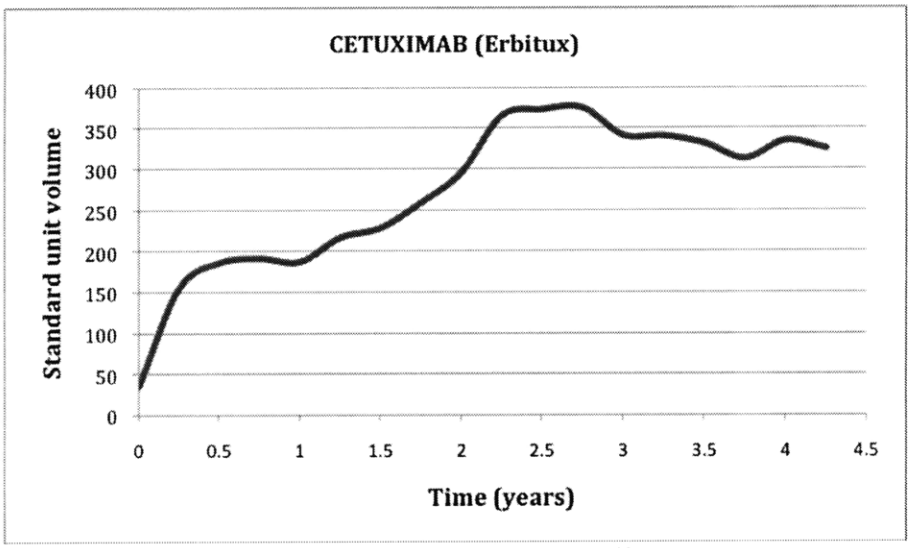

Figure 7: Erbitux – Standard unit volume over time[42]

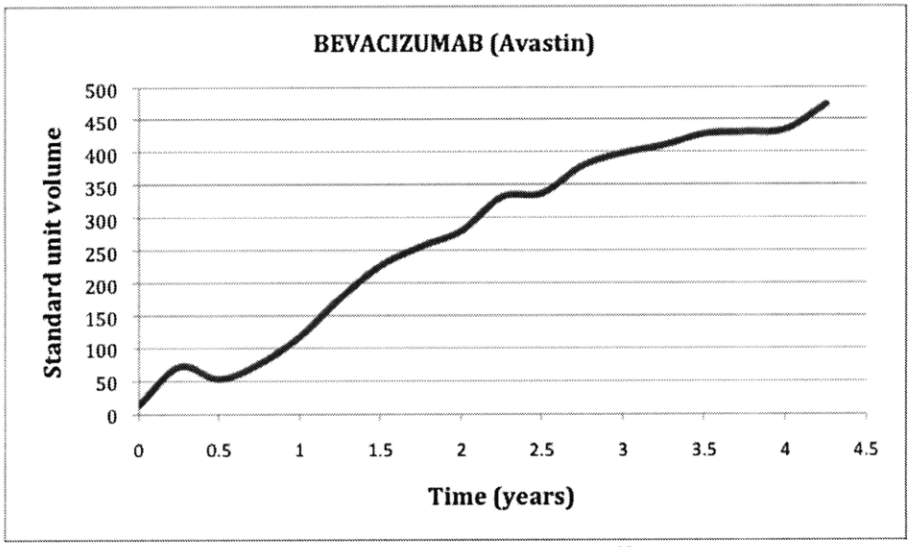

Figure 8: Avastin – Standard unit volume over time[42]

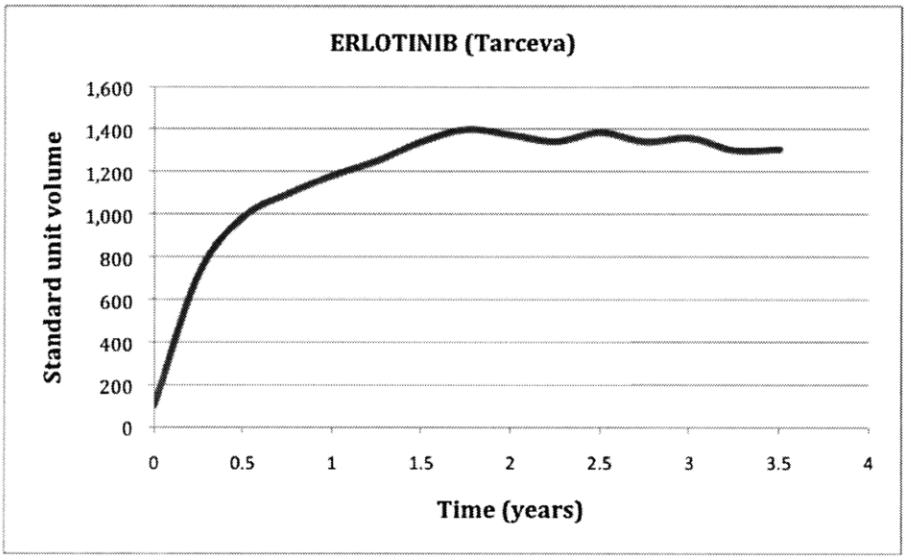

Figure 9: Tarceva – Standard unit volume over time[42]

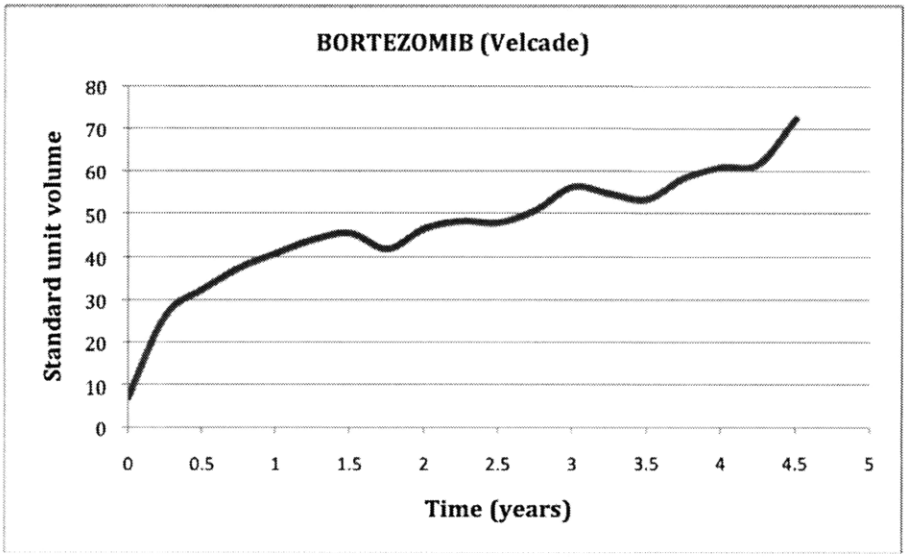

Figure 10: Velcade -Standard unit volume over time[42]

The adoption velocity for Erbitux over its life (4.25 years) is 17%; for Avastin over its life (4.25 years) is 27%; for Tarceva over its life (3.75 years) is 16%; for Velcade over its life (4.75 years) is 15%. For all new stratified drugs, this gives a mean adoption velocity over the life of drug since launch of 19%, with a SD of 5%.

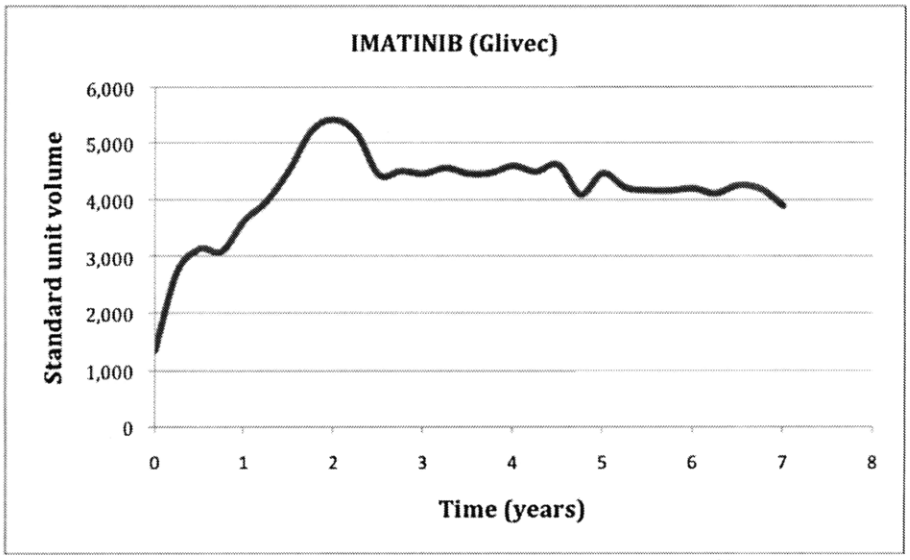

Figure 11: Gleevec chart – Standard unit volume over time[42]

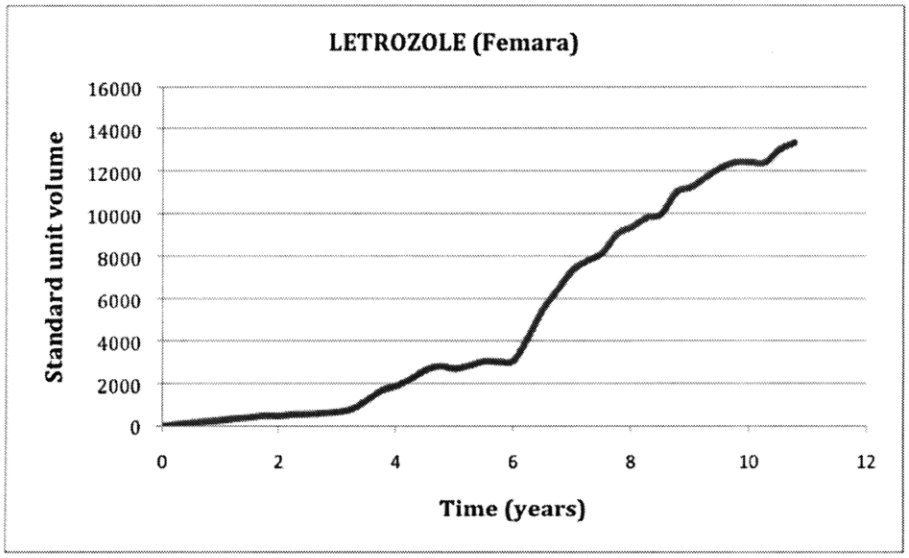

Figure 12: Femara – Standard unit volume over time[42]

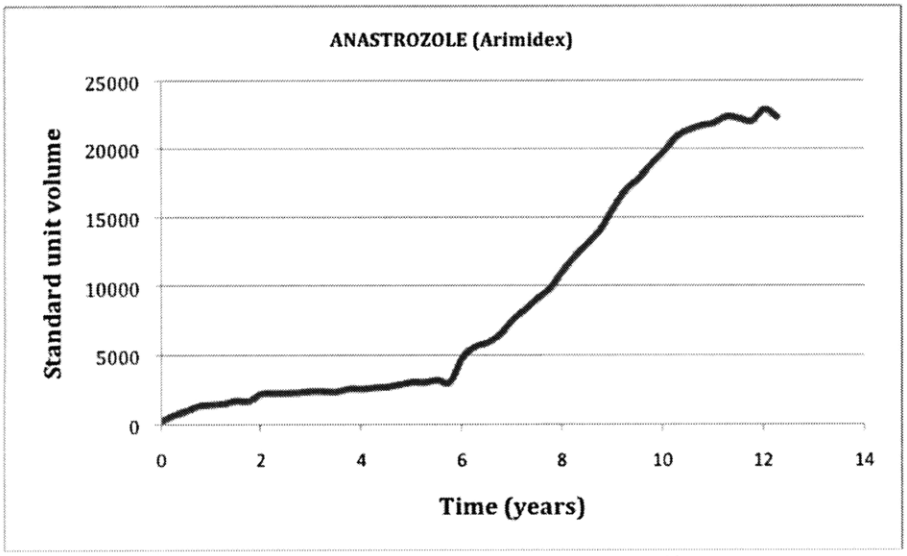

Figure 13: Arimidex – Standard unit volume over time[42]

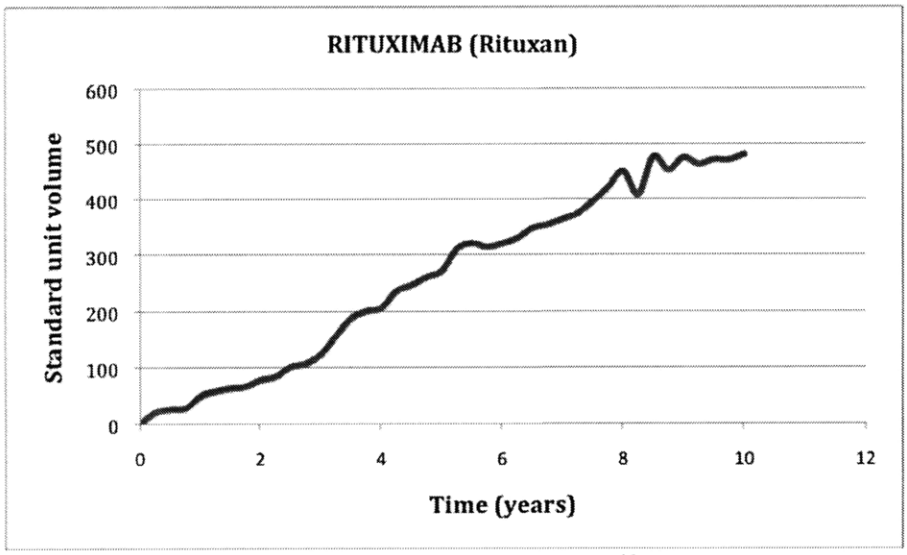

Figure 14: Ritxan – Standard unit volume over time[42]

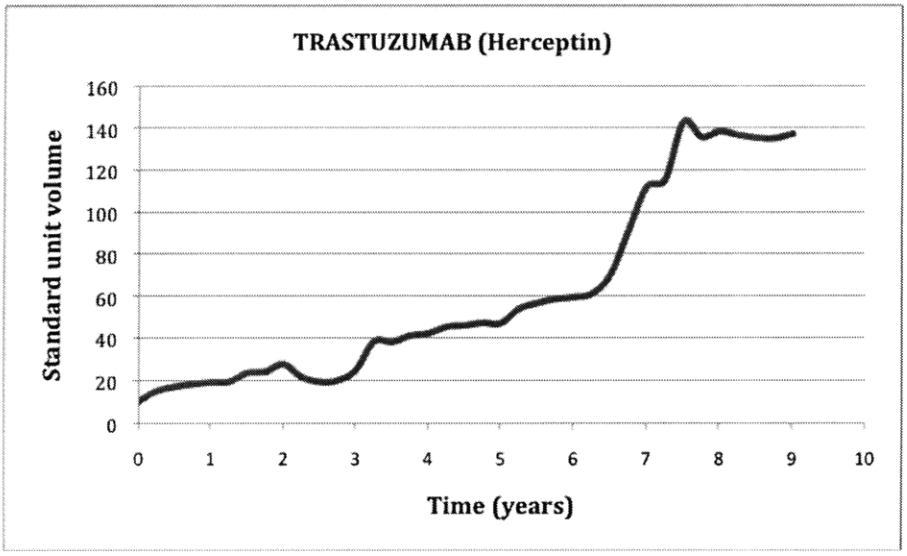

Figure 15: Herceptin - Standard unit volume over time[42]

The adoption velocities over the first four years for mature stratified drugs are 11% for Gleevec, 20% for Arimidex, 20% for Femara, 24% for Rituxan and 16% for Herceptin. This yields an average adoption velocity over the first four years of life of 18%, with a SD of 5%. Compared to the average profile of the newer drugs (mean 19%; SD 5%) it appears that the growth profiles of the newer stratified medicines are very similar to those of the very first stratified products launched eight to ten years ago.

The adoption velocities over the life of the mature stratified drugs were 11% for Gleevec, 3% for Femara, 2% from Arimidex, 10% for Rituxan and 5% for Herceptin. This resulted in an average adoption velocity for the mature stratified drugs of 6%, and a standard deviation of 4%.

The time to peak unit volume for each of the mature drugs was 2 years for Gleevec, 12 years for Femara, 12 years for Arimidex, 8.5 years for Rituxan and 6.25 years for Herceptin.

The Impact of Gleevec

It is clear that Gleevec has different characteristics from the other stratified therapeutics in this data set. It can be seen from the graph above that although the adoption velocity in the first four years is 11%, this does not tell the whole story as clearly the adoption velocity in the first two years was more in the order of 30-40% after which sales leveled out. When Gleevec was launched it was hailed as the first 'rationally' designed drug[32] targeting a specific pathway (bcl-able kinase) and thus generated huge publicity. Combined with the fact that it was the first drug to be truly effective in chronic myelogenous leukemia, this may account for its initial meteoric growth rate. Although Gleevec is considered under this analysis to be a mature drug, it has only been on the market for 7.5 years, and it remains to be seen what its long-term growth profile looks like. For these reasons I decided to exclude Gleevec from the collated data. This resulted in a mean adoption velocity over the lifetime of the remaining mature drugs (Femara, Arimidex, Rituxan and Herceptin) of 5%, with a SD of 3.7%; the mean adoption velocity in the first four years excluding Gleevec is 19.8%, with a SD of 3.3%.

2.4 Discussion

The primary purpose of this analysis is to establish whether the growth profile of stratified drugs is significantly different from that of traditional, gold-standard chemotherapeutics. I use this measure as a proxy to evaluate whether stratified

medicines establish market penetration at a slower, equivalent or faster rate than traditional, gold-standard therapeutics.

One challenge highlighted as a result of this analysis is that in most cases, traditional chemotherapeutics have been on the market longer than stratified medicines. Even mature stratified therapeutics are still being investigated for new indications, some of which could have significant potential and could result in a resurgence of growth. For example, Taxotere, a mature chemotherapeutic was approved for head and neck cancer in 2007[33]. Due to this, the use of adoption velocities over the life of a drug until the time when peak unit volume is reached may not in fact be when peak unit volumes are reached. Using mature drugs as an example this phenomenon is demonstrated in the graph below.

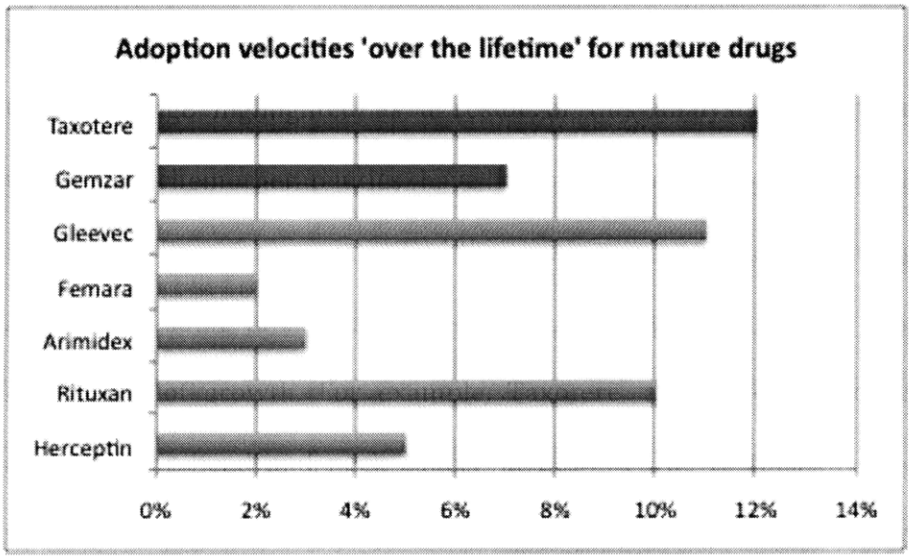

Figure 16: Adoption velocities over lifetime (mature drugs) (Stratified in blue)[42]

Looking at time to peak unit volume for all mature drugs is also useful:

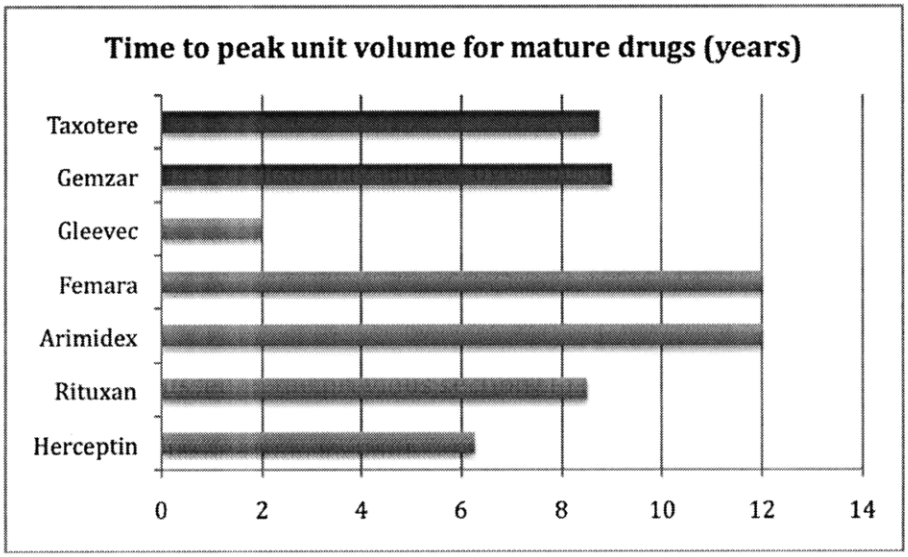

Figure 17: Time to peak unit volume in years (mature drugs) (Stratified in blue)[42]

These statistics paint an incomplete picture. On the one hand, when analyzing adoption velocities, Taxotere, arguably the best traditional chemotherapeutic ever developed, has a clear advantage over blockbuster drugs such as Rituxan and Herceptin. The breast-cancer drugs (Arimidex and Femara) lag behind in the case of both adoption velocities and time to peak unit volume. Gleevec is an anomaly (for reasons discussed in the previous section) in both sets of data.

If forced to draw a conclusion based on adoption velocity data, the data show that the mean adoption velocity until peak unit volume of stratified drugs (excluding Gleevec) is 5% with a SD of 3.7%, and for non stratified drugs is 10% with a SD of 3%.

Given the unknowns introduced by the fact that all drugs may have many more indications to be approved, and additional time therefore to grow and reach new

levels of peak unit volume, I decided to examine the adoption velocity for both new and mature drugs in the first four years of life.

The first four years of a drug's life are arguably the most critical, It is a period in which the greatest growth should occur, where physicians belief (or lack thereof) of the data generated in clinical trials is vindicated, the result of hundreds of millions of dollars in marketing spend. In short, the first four years are a key indicator of the future performance of a drug, and therefore can be used to examine equivalence amongst the chosen drugs.

When comparing the first four years of adoption velocity, the story looks somewhat different.

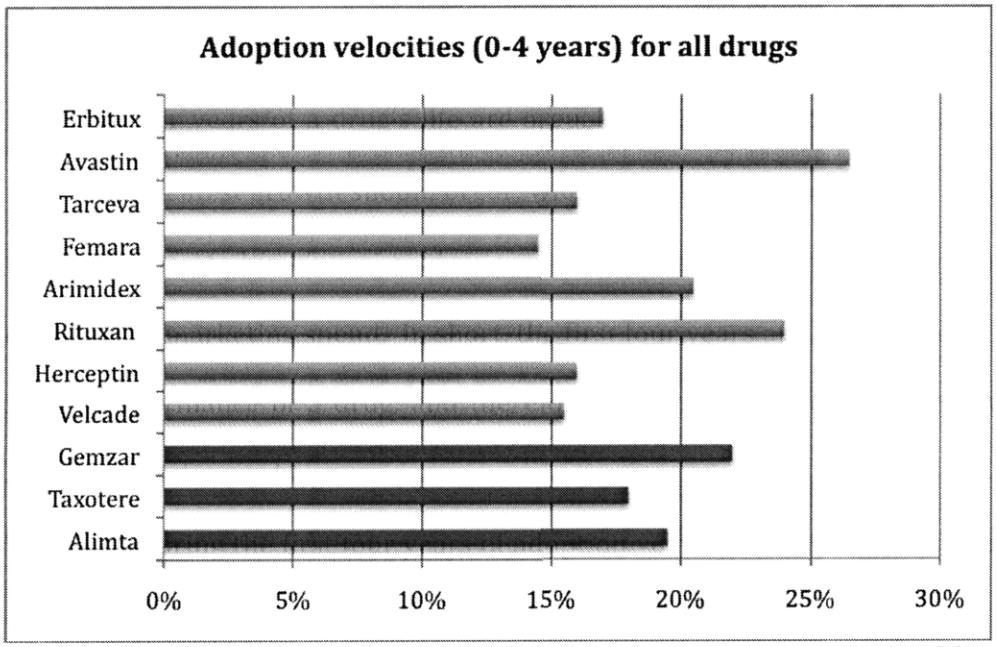

Figure 18: Adoption velocities (0-4 years) for all drugs (stratified in blue)[42]

This graph shows that many of the stratified therapeutics are close to, and in some cases (Rituxan and Avastin) exceed the adoption velocities of traditional

chemotherapeutic drugs. Overall, the mean adoption velocity for stratified drugs is 19.4%, with a SD of 4.1% whereas with non-stratified drugs the mean adoption velocity is 19.8% with a standard deviation of 1.7%.

It was not informative to test the null hypothesis of equal growth rates as due to the small sample size the power to reject the null hypothesis was unacceptably low.

Femara and Arimidex

It can be seen from the data that both Femara and Arimidex show similar profiles. They are both aromatase inhibitors indicated in the adjuavant therapy of hormone-receptor breast cancer patients.

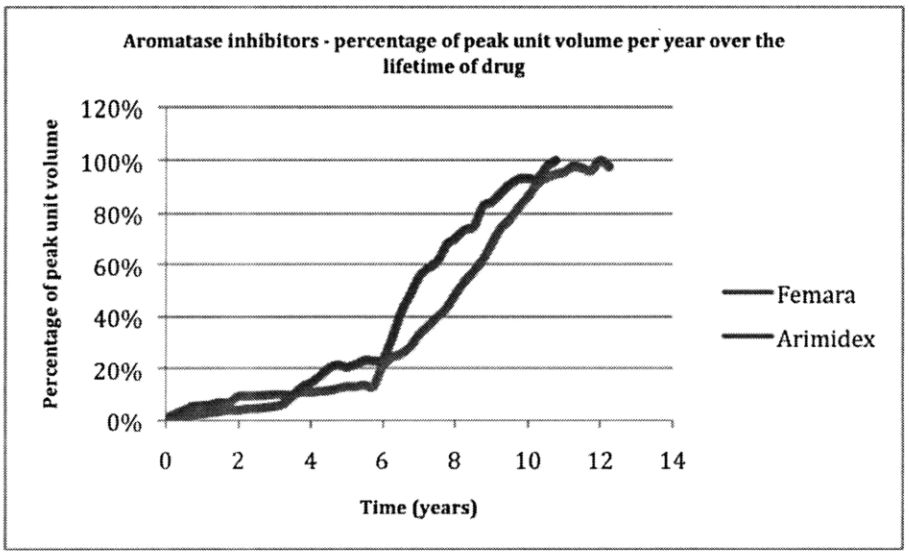

Figure 19: Aromatase inhibitors - percentage of peak unit volume per year over the lifetime of drug[42]

Both drugs display a similar growth profile when looking at percentage of peak unit volume per year over the lifetime of the drug. Both drugs achieved a 0-4 year

adoption velocity of 20%, and an adoption velocity over the life of each drug of 3% (Femara) and 2% (Arimidex). Each drug took approximately 12 years to reach peak unit volume.

The reason this may be of interest is because as well as having the same indications, both drugs' mechanism of action iss targeted against the same enzyme, aromatase (converts androgen to estrogen). This is relevant because firstly, there is much interest in developing cancer therapeutics based on molecular targets as opposed to organ, and secondly, some stratified drugs, such as Rituxan and Herceptin, have many follow-on therapeutics in the pipeline. That this finding may have relevance to the commercial departments of entities developing these drugs, I believe warrants further investigation.

2.5 Summary

The data indicates that although over a long term horizon (over the life of each drug) non-stratified therapeutics are more successful in terms of growth and therefore market penetration, this assumption may be mistaken due to the fact that non-stratified drugs have had longer lifetimes and that mature stratified drugs may indeed have further growth spurts due to future approvals in additional indications.

Shorter term data, looking at the critical 0-4 year adoption velocity of each drug indicates that there is indeed rough equivalence between stratified and non-stratified drugs, with average adoption velocities of 19.4% and 19.8% respectively. A similar level of growth during this stage is an important finding as it addresses

concerns that stratified drugs may perform more poorly than their gold-standard chemotherapeutic peers due to reluctance by oncologists to switch to new therapies. Indeed, as stratified medications are developed by design rather than by accident, as were many of the initial stratified drugs, the concept of stratification is likely to become better accepted and established, leading to potentially faster market adoption.

Finally, the findings with Arimidex and Femara, two drugs which have similar targets, indications and growth profiles, indicate that further investigation may be warranted in order to predict the future growth profiles of follow-up therapeutics to popular biologics such as Rituxan and Herceptin.

3.Investment Analyst and Industry Interviews

As part of primary research into the stratified medicine space, and because of concerns raised regarding the economic implications of developing and marketing stratified therapeutics, I interviewed a number of Wall Street investment analysts to garner their views on stratified medicine. The analyst interviews were supplemented by ad hoc interviews of industry employees at the JPMorgan Healthcare Conference in January 2009. A copy of the interview guide can be found in the appendix. The interviews were semi-structured – i.e, each section is loosely based around the questions asked in the interviews.

The interviewees were selected in collaboration with the investor relations group of Eli Lilly and Co, and criteria included seniority (full analyst), institution (top tier) and coverage of companies involved in stratified medicine. The interviews were conducted via conference call and included the author, Mark Trusheim, Jim Griffet (Eli Lilly) as well as the interviewee. The interviews were conducted between 16th-20th May 2008 and each lasted approximately one hour.

What is a 'Stratified Medicine?'

The general definition of stratified medicine was aligned across interviewees with the focus on a therapeutic that is dependent to some degree on a companion diagnostic to predict efficacy or adverse side effects. The response to the question encompassed therapeutic areas beyond oncology with one interviewee mentioning

'even hypertension' could be a target for stratified medicine, and another that without a companion diagnostic it could be 'difficult' to get a new therapy to market.

Examples of Stratified Medicine

The interviewees gave varied responses for examples of stratified medicine, with the common theme being molecular or genetic biomarkers. In the oncology space, responses included:

- BRCA Test (Myriad Genetics)
- Oncotype Dx (Genomic Health)
- Mammoprint (Agendia)

Examples outside of oncology included:

- ApoE and Tau (Alzheimers)
- Warfarin metabolism
- High Risk Plaque (HRP) test
- Statin tests
- Liver tests

Companies that were described as being active in the space included the following that were covered by at least one of the analysts:

- Affymetrix
- Illumina

- Charles River
- Applied Biosystems

Predictably, Roche was mentioned as being relevant to the space due to its strength in diagnostics, with one analyst specifically mentioning its development of leukemia markers. Johnson & Johnson, BMS and Abbott were also identified as being focused to some degree on earlier development of biomarkers. One analyst mentioned that 'Steve Paul at Lilly cited that over 50% of their therapies are/will be targeted in the near future.'

Interestingly, relatively little was mentioned in any of the interviews about drugs such as Herceptin. Rituxan, Gleevec etc, which was surprising given the attention they receive as the heralds of stratified medicine. The focus was more on the development of actual biomarkers themselves.

Key Big Pharma groups mentioned as leaders in the space of biomarkers including the following:

- Roche
- Eli Lilly
- Johnson & Johnson
- Abbott
- Bristol Myers Squibb

The Economics

A key concern is the business model of a diagnostic/biomarker developed in terms of generating revenue. One analyst with a focus on molecular diagnostics did not believe that the biomarker total market size would exceed $200mn/year per marker, and that all diagnostic tests would eventually become commoditized.

Pharmaceutical companies contracting with diagnostics companies appeared to be the most popular choice of relationship, but with the caveat built in that pharma would need to find a mechanism to share risk with the diagnostic companies, given the discrepancy between the size of upside for a diagnostic versus a therapeutic. Factors that could play into this included use of a diagnostic to strengthen the IP position of a drug.

An interesting observation was that biomarkers may not necessarily be attractive for established diagnostics players, due to the fact that they have a 'therapeutic-like' profile (despite lower clinical/regulatory risk). This may spawn a new breed of companies developing just biomarkers on a contract basis, though in this case the same business model issues apply. It was mentioned that VCs find the molecular dignostics/biomarker space interesting, but do not have a good handle on when may be the right time to invest.

Payers

Interviewees did not have much technical insight into the potential behavior of payers but voiced several opinions. These included the view that payers would find stratified therapeutics attractive if they demonstrably performed better than their non-stratified counterparts, and that a biomarker would allow a drug to move up within formulary rankings. On the flipside, the 'uncertainty' factor of stratified medicines was mentioned as a reason why payors may not adopt, particularly given that prices may be higher. The NICE (UK) Velcade story was mentioned as a potential path whereby pharma companies perform pharmacoeconomic studies to demonstrate overall cost effectiveness.

Ultimately all interviewees stated that CMS would not be able to say no to good new therapeutics and that the cardiovascular and oncology spaces were most likely to benefit.

FDA

The almost universal view was that stratification of therapies and the use of biomarkers was attractive to the FDA. Legacy stratified therapeutics such as herceptin are often the result of rescue strategies for drugs that have otherwise failed. This will change as companies incorporate biomarkers into their R&D strategy, and is likely to be supported by the FDA.

Other Comments of Note

A common concern amongst all interviewees was the inherent conflict between commercial and R&D arms of big pharmaceutical companies. Commercial groups have historically been averse to stratified medicines as they carry the perception of smaller market sizes and overall less favorable economics. R&D groups focused on scientific progress have felt inhibited by restrictions from commercial colleagues.

This is changing at some big pharmaceutical companies such as Eli Lilly, where significant portions of the R&D portfolio are now stratified, but pharma as a whole has yet to accept stratified medicine as an economically feasible path. They should however be reassured by the financial performace of drugs such as Herceptin, Gleevec and Rituxan, all of which could be considered blockbusters by all metrics.

Interviews given by individuals from Leerink Swan, SG Cowen, Lehman Bros, Pfizer and small-cap Boston-based life sciences companies were collated to provide the above overview

4.Future Clinical Biomaker Scenario Modelling

4.1 Description of model

As part of the broader Center for Biomedical Innovation Stratified Medicine effort, a predictive stratified medicine model has been developed. The development of this model has been led by Mark Trusheim, and supported by Sameer Sabir, James Cho and Ernst Berndt.

The model was used for the purposes of this thesis to analyse the impact of biomarkers and their efficacy from an economic and ethical viewpoint. The model contains sophisticated functionality, of which a small component was utilized. The purpose of this section is to give an overview of the structure of this model, and an indication of the features used, as well as specific inputs used for the thesis research. The model is written in Excel and is based on the use of patient populations broken down into 'responders' and 'non-responders'. In an ideal world this would be a bimodal distribution. However, to reflect the real world the model has the capability to provide overlapping patient populations and the ability to adjust the biomarker cut-off values:

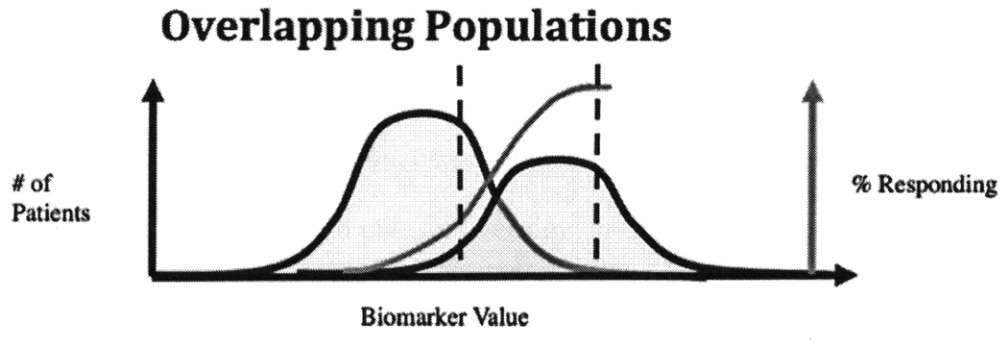

Figure 20: Non-responders (left), responders (right) with dotted lines showing potential cutoff values for the biomarker test.

The primary purpose for using the model in this thesis is to investigate the impact of 'biomarker polluters' within the pool of patients on both the economic and ethical issues. This will be discussed in further detail.

The model contains a discrete set of inputs and outputs, as follows:

	Input	**Output**
Biomarker Performance	Percent responder	Sensitivity
	Separation of populations	Specificity
	Biomarker cut-off	NPV, PPV
Population Enrichment	Population Distribution (passed)	Selected population therapeutic effect
	Biomarker performance (polluter percentage)	
	Responder therapeutic effect	
Therapeutic Performance and Adoption	Selected population effect (passed)	Adoption speed
	Adoption speed	Peak market share
	Peak market share	
	Therapeutic performance differential	
Adoption Curve	Selected adoption speed (passed)	Market share over time
	Selected market share (passed)	
	Linear/logistic curve	
Market Size for Therapeutic and Diagnostic	Biomarker selected %	All passed to market position
	Prevalence and Incidence	
	Patient population growth	
	Current addressable market	
	Future addressable market	
	% of diagnostic qualified patients put on therapy	

	% of patients monitored by diagnostic	
	Blockbuster reference values for speed, share, price	
Pricing	Selected popuation effect (passed)	Scenario specific drug and diagnostic prices
	Drug performance pricing table	
	Base drug and diagnostic prices	
	Price premium (override)	
Market Position for Drug and Diagnostic	Passed: Peak share, adoption speed, market sizes, diagnostic use, pricing, blockbuster reference (passed)	Patients tested and treated over time
		Sales over time for drug/diagnostic
		Reference blockbuster sales and patients
Financial Results: Summary Devt costs	Start year, patent life remaining, approval year, drug and diagnostic development costs	Marketing years Development costs over time
Financial Results	Devt costs/sales (passed)	Combined cash flows
	COGS and SGandA pct of sales for drug and diagnostic, discount rate	NPVs for drug, diagnostic, combination

Table 2: Model inputs and outputs

Model Flow

The model is structured to flow as follows:

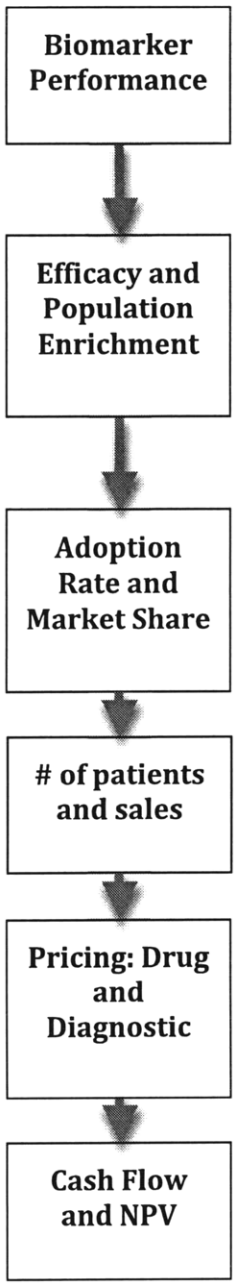

Figure 21: Model Flow

4.2 Description of Scenarios

The primary objective of this section of the thesis is to investigate the impact of biomarker efficacy, specifically the percentage of 'polluters,' or individuals who are 'non-responders' but are included in the pool of patients to whom therapy is provided, based on the test results of the clinical biomarker.

The impact of biomarker efficacy takes two forms for the purpose of this study – economic impact, including market share, net present values etc, and the consequent ethical issues that arise from these results.

In order to develop realistic but consistent scenarios, it was decided to hold a significant number of parameters constant across all scenarios. These uniformly constant parameters included:

Indication Market Size

	Current Value
Prevalence (in launch yr)	0
Switching % (Other treatments)	0%
Switching Out % (Drug)	100%
Incidence (per year in launch yr)	200,000
Patient Growth Rate	2%
Current Addressable	100%
Future Additional Addressable	0%
Diagnostic Test Population	

% Qualified Patients Treated	80%
% on Treatment Monitored	50%
# Monitoring Tests / Yr	$ 2

Table 3: Parameters fixed over all scenarios

The constant values reflect the assumption that patients, once on drug, will maintain treatment on drug and not switch out to another drug. The incidence is taken to be 200,000 with a growth rate of around 2%, which reflects the approximate annual incidence (178,000 in 2007) and growth rate of invasive breast cancer[39]. I assume that the entire universe of breast cancer sufferers is 'addressable' meaning that they are eligible to take the diagnostic test. I also assume that given the high likelihood that a patient who tests positive in the biomarker will take the drug, that the percentage of qualified patients treated is 80%. I assume that each patient will receive two monitoring tests per year.

Commercial Costs

	Therapeutic	Diagnostic
Cost of Goods Sold (COGS) % of Sales	20%	30%
Selling, General and Adminstration (SG&A)% of Sales	30%	20%

Table 4: Development Costs

COGS and SG&A for the therapeutic were approximated using revenue, COGS and SG&A numbers from Genentech 2008 financial results. [40]

COGS and SG&A for the diagnostic were approximated using ratios from Monogram Biosciences[41]

Financial Results

The discount rate was kept constant at 12% across all scenarios. The diagnostic cost was kept constant at $500.

The scenarios were defined by the parameters price, % responders and % polluters in the following manner:

	Price of therapy($)	% Responders	Separation	Biomarker cut-off	% Polluters
Scenario 1	10,000	20	30	55	3.87
Scenario 2	10,000	20	30	43	30.57
Scenario 3	10,000	65	30	44	4.77
Scenario 4	10,000	65	30	31	20.58
Scenario 5	30,000	20	30	54	4.81
Scenario 6	30,000	20	30	43	30.57
Scenario 7	30,000	65	30	44	4.77
Scenario 8	30,000	65	30	31	20.58

Table 5: Biomarker values

Scenarios 1,3,5 and 7 have a small number of polluters and are intended to represent 'very accurate' biomarkers. Scenarios 2,4,6 and 8 have a larger number of polluters and are intended to represent 'less accurate' biomarkers.

The following terms will be used in the analysis, and can be classified as follows:

Classification	Scenarios
Price – Low	1-4

Price – High	5-8
Responders – Low	1,2,5,6
Responders – High	3,4,7,8
Polluters – low	1,3,5,7
Polluters – high	2,4,6,8

Table 6: Classification and Scenarios

The scenarios were selected in order to enable a thorough examination of the relationships amongst price, % of responders and % of polluters, and their impact on economic and subsequently ethical factors. Following is a graphical representation and brief description of each scenario.

In each scenario, the curve to the left portrays non-responders, the curve to the right are responders, and the dotted line indicates the biomarker cutoff. Patients in the model are on drug until death.

The rationale behind the scenarios is to examine the relationships among price, percentage of responders, and percentage of polluters. Scenarios 1-4 use a price point of $10,000/year/patient. Scenarios 1 and 2 have a low percentage of responders. In scenario 1 the percentage of polluters is low, and in scenario 2 the percentage of polluters is high. Scenarios 3 and 4 have a high number of responders. In scenario 3 the number of polluters is low, and in scenario 4 the number of polluters is high. In scenarios 5-8 the same pattern is repeated but using a higher price point of $30,000/year/patient.

The impact of these factors on the number of patients on drug and diagnostic, and the resultant revenues and cash flow generated, will be examined in detail. As both the percentage of responders and the percentage of polluters impact the number of patients who receive drug, I expect to observe that in the scenarios with low numbers of responders and polluters, the potential revenues, cash flows and resultant net present value of the drug/diagnostic combination will be low due to the limited number of patients. In scenarios with high numbers of responders and polluters, the potential revenues, cash flows and resultant net present value of the drug/diagnostic combination will be high due to the higher number of patients. I also expect price to have an impact on these factors and hope to show that the ability to charge a higher price leads to a more attractive drug. I expect to see that the most attractive combinations will be a highly priced drug with a high number of responders and polluters. Therefore the tradeoff that will be explored is that a biomarker that is extremely effective is unlikely to result in a commercially attractive drug, and in order to ensure commercial viability, a biomarker will need to be 'just good enough.' I hope, through multiple combinations of all these parameters, to create a gradient of net present values through the eight scenarios and thereby gain an understanding of what the 'sweet spot' may be for a pharmaceutical industry in this complex equation.

4.3 Graphical Representation of scenarios

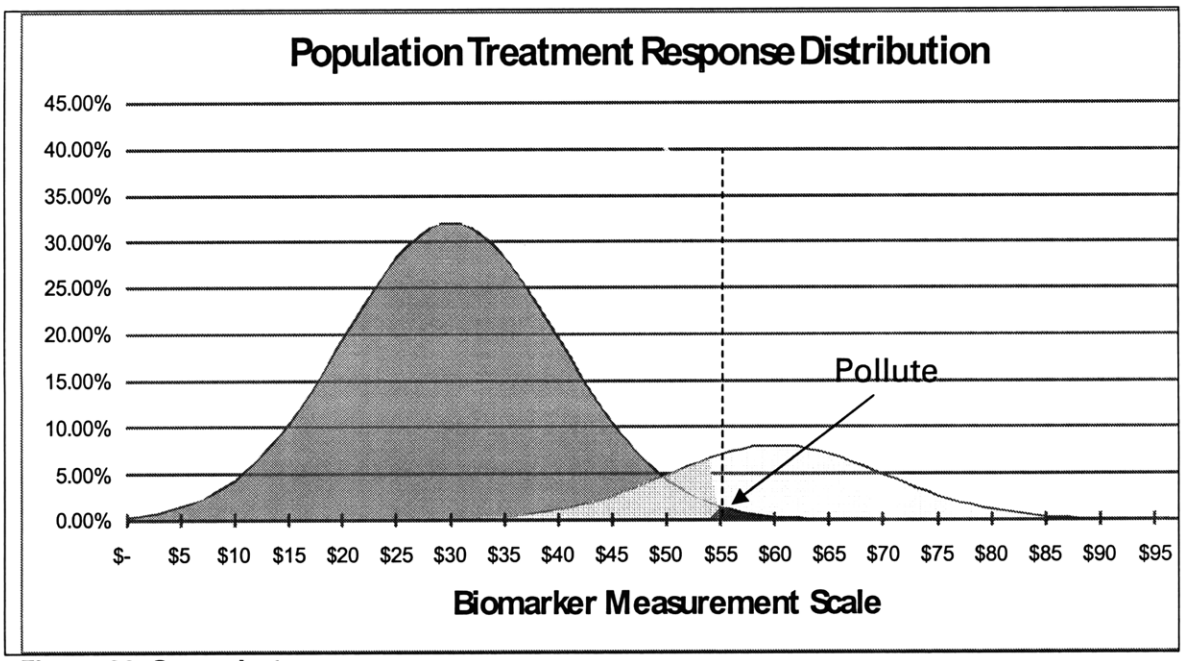

Figure 22: Scenario 1

Scenario 1 represents a low-priced drug in which the biomarker has a low responder rate and a low polluter rate, resulting in a small patient population. Price: $10,000 (low); Responder rate 20% (low); Polluter percentage 3.87% (low)

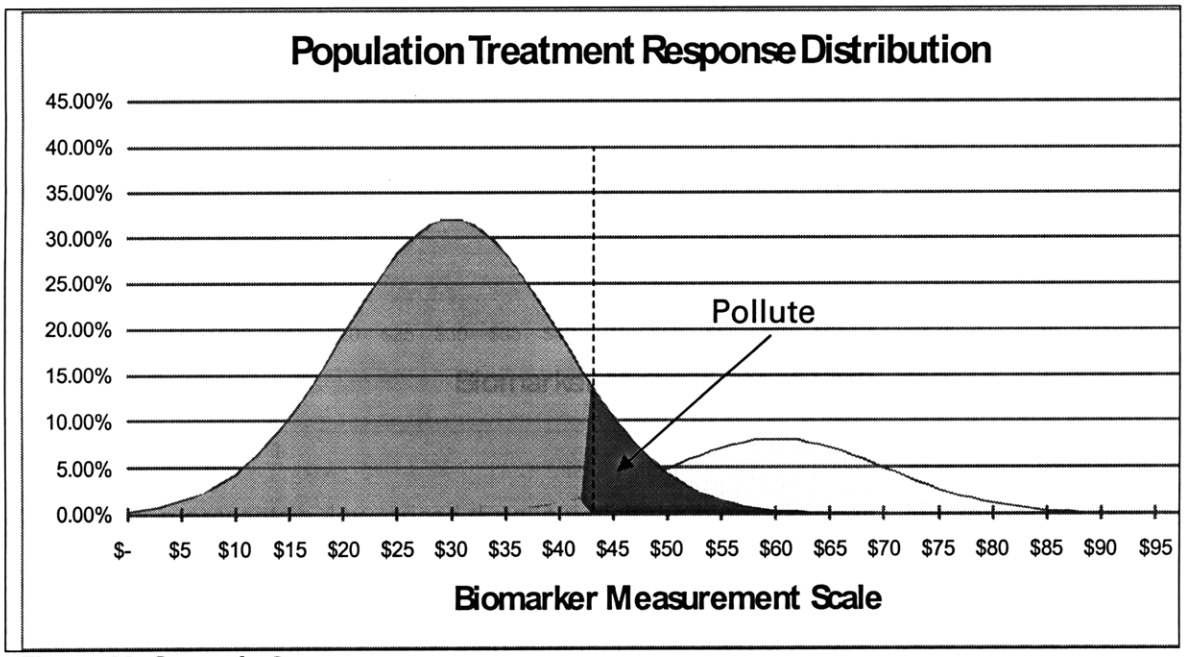

Figure 23: Scenario 2

Scenario 2 represents a low-priced drug in which the number of responders is low, but the number of polluters is high, thus resulting in a larger patient population than scenario 1. Price $10,000 (low); Responder rate 20% (low); Polluter percentage 30.57% (high)

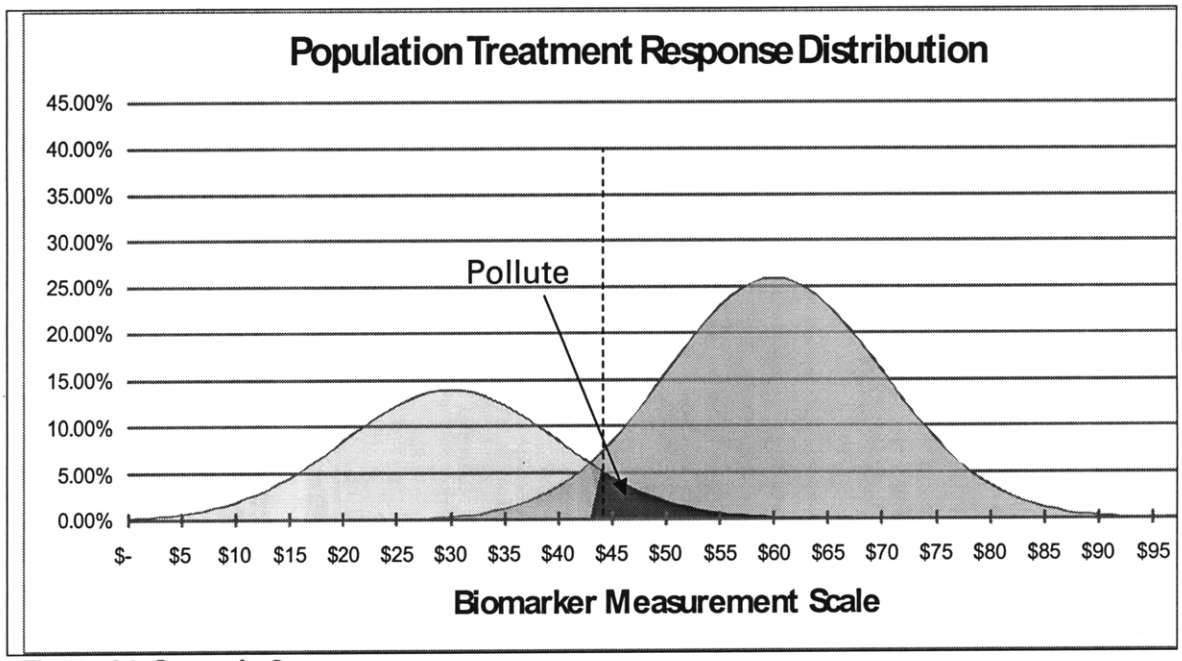

Figure 24: Scenario 3

Scenario 3 represents a low-priced drug but with a larger percentage of responders and a small percentage of polluters. The result is a drug which works in a larger proportion of the patient population, but has a very accurate biomarker. Priced $10,000 (low); Responder rate 65% (high); Polluter percentage 4.77% (low)

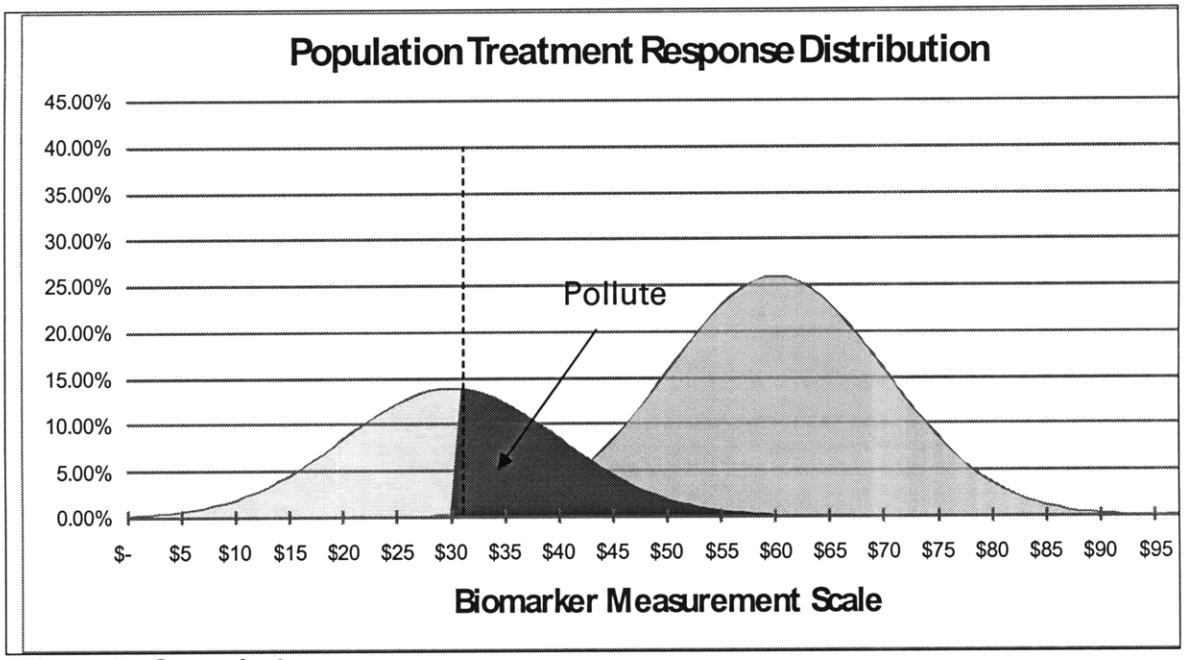

Figure 25: Scenario 4

Scenario 4 represents a low-priced drug with a large percentage of responders and a large number of polluters, resulting in a large patient population receiving drug, Price $10,000 (low); Responder rate 65% (high); polluter percentage 20.58% (high)

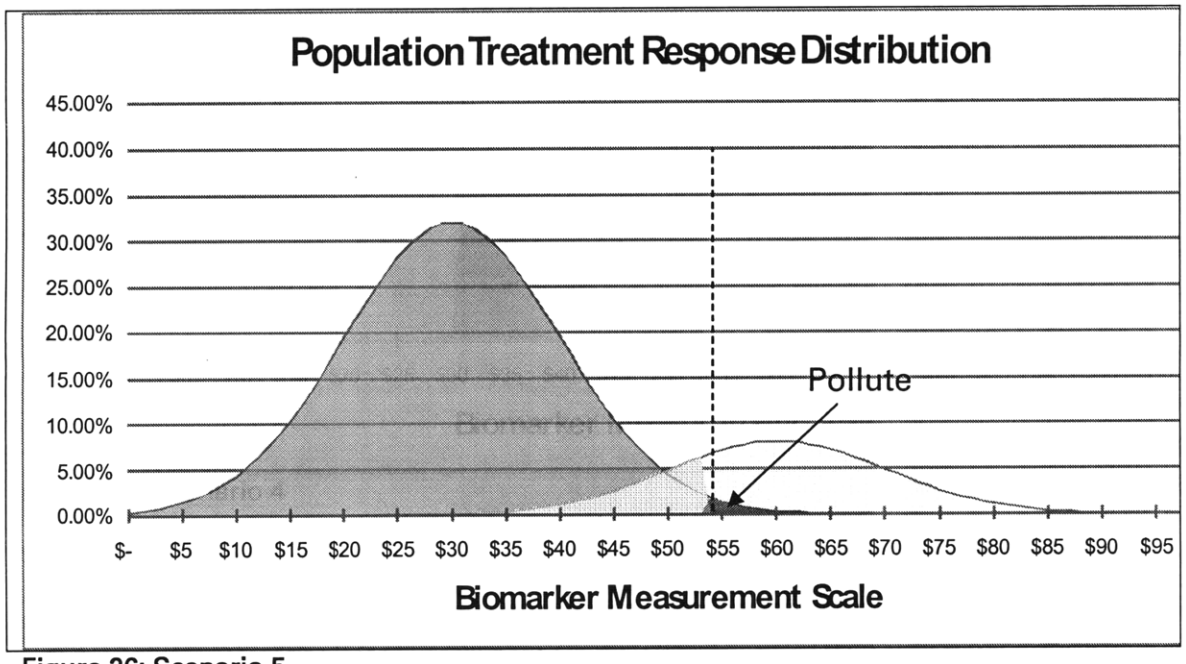

Figure 26: Scenario 5

Scenario 5 represents a high priced drug effective in a small percentage of the total patient population and with a low number of polluters due to a very effective biomarker. Price $30,000 (high); Responder rate 20% (low) polluter percentage 4.81% (low).

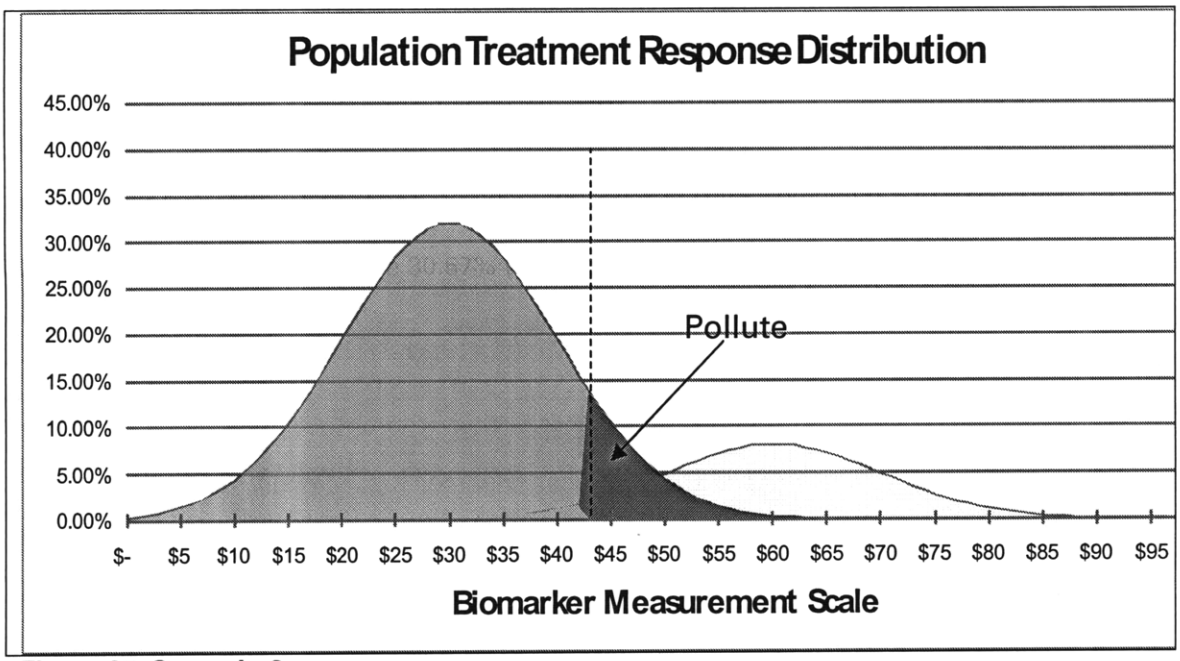

Figure 27: Scenario 6

Scenario 6 represents a high-priced drug which is effective in a small percentage of the population but has a large number of polluters due to a less sensitive biomarker, and therefore a larger number of patients than scenario 5. Price $30,000 (high); Responder rate 20% (low); Polluter percentage 30.57% (high)

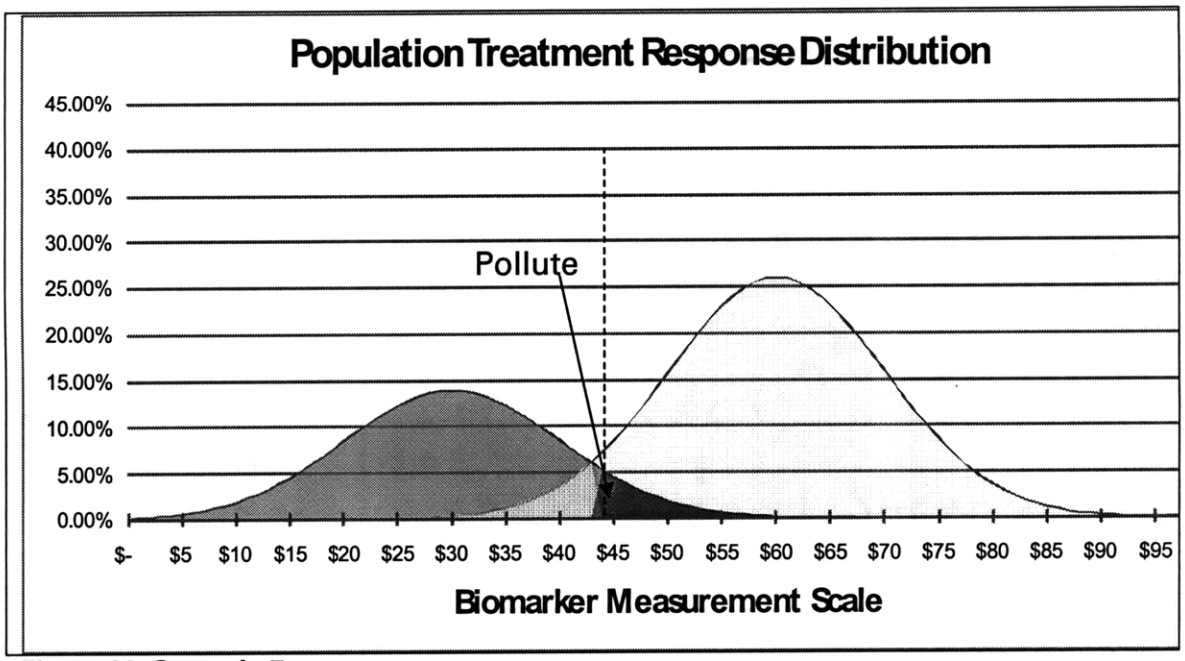

Figure 28: Scenario 7

Scenario 7 represents a high-priced drug which is effective in a small percentage of the population, but has a very effective biomarker and therefore a low percentage of polluters. Price $30,000 (high); Responder rate 65% (high); Polluter percentage 4.77% (low)

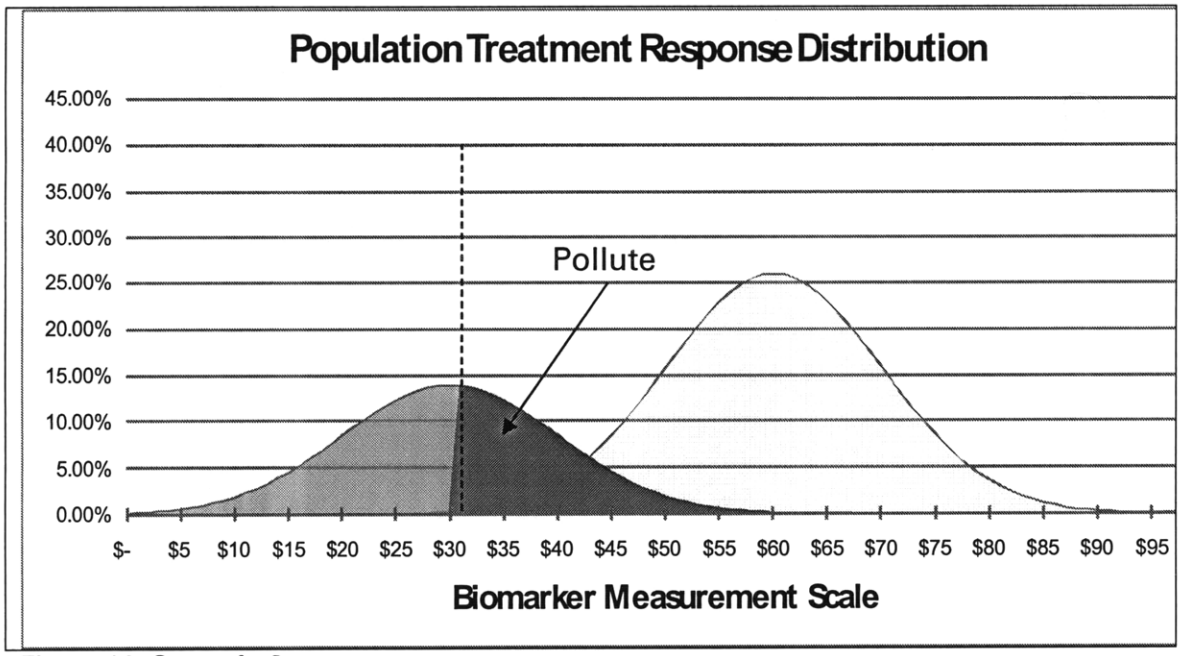

Figure 29: Scenario 8

Scenario 8 represents a high-priced drug which is effective in a large percentage of the population and has a high number of polluters resulting in a large patient population. Price $30,000 (high); Responder rate 65% (high); Polluter percentage 20.58% (high)

4.4 Discussion of results from Modeling Scenarios

The outcome of each scenario will be outlined individually. The primary outcome measures for each scenario are:

- Number of patients on drug and diagnostic (annual basis) 0-10 years from launch
- Revenues of drug and diagnostic (annual basis) 0-10 years from launch
- Net present value of drug, diagnostic and drug + diagnostic
- Operating cash flow of drug and diagnostic (annual basis) 0-10 years from launch

Explanation of chart legends

These scenarios were developed using the predictive stratified medicine model developed at the Center for Biomedical Innovation (CBI). The data in this section for each scenario is displayed in the form of two charts. The legend for each chart is explained below. It should be noted that the legend in each chart displays *all potential* parameters that can be calculated. In this research only selected parameters were used. However due to the structure of the model it is only possible to display *all potential parameters*, not solely selected parameters. Only legends for displayed (selected) legends are described below.

- Market Position Chart displays patient and sales data from each scenario.

  Legends incude:

  - Patients Drug Log: Number of patients on drug (thousands)
  - Sales Drug Log: Revenue from drug ($mn)

- Diagnostic Drug Log: Number of patients who receive diagnostic test (thousands)
- Sales Diag Log: Revenue from diagnostic ($mn)

- Financial results displays operating cash flow for both drug and diagnostic from each scenario
  - CF Drug Log: Cash flow from drug ($mn)
  - CF Diag Log: Cash flow from Diagnostic ($mn)

All other parameters displayed in the legend bar are not displayed on the charts.

Definition of terms

Positive Predictive Value – is the proportion of patients with positive test results who are correctly diagnosed.[48]

Negative Predictive Value – is the proportion of patients with negative test results who are correctly diagnosed. [49]

Sensitivity - is the proportion of actual positives who are identified as such[51]

Specificity – is the proportion of actual negatives who are correctly identified as such.[50]

		Condition		
		Positive	**Negative**	
Test outcome	**Positive**	True Positive (a)	False Positive (b)	= Positive predictive value (a/a+b)
	Negative	False Negative (c)	True Negative (d)	= Negative Predictive Value (d/c+d)
		=Sensitivity (a/a+c)	=Specificity (d/b+d)	

Table 7: Relation between positive predictive value, negative predictive value, sensitivity and specificity[48]

Scenario 1

A low percentage of responders (20%) and polluters (3.87%) results in an 'accurate' biomarker that is highly selective for patients that are likely to respond to the given therapeutic with a high specificity of 99.29%, a moderate sensitivity of 70.89%, a high negative predictive value of 96.13% and a high positive predictive value of 93.17%. The number of 'false positives' or patients, who are non-responders but slipped through the net, is low. With the price point at $10,000, the net present value for the therapeutic in this given scenario is $-280.60mn, the biomarker $89.9mn giving a total net present value of $-190.8mn.

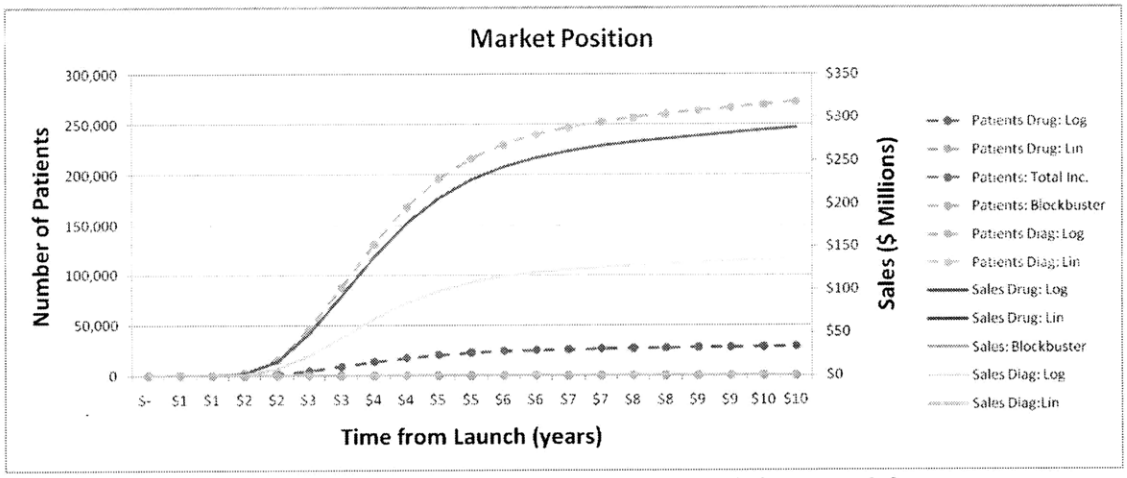

Fig 30: Scenario 1: No. of patients and sales (drug and diagnostic)

The market position chart demonstrates that with these parameters, 10 years from launch only around 30,000 patients actually end up on drug. At the $10,000 price point, this represents only around $250mn in revenue, and around $130mn in operating cash flow.

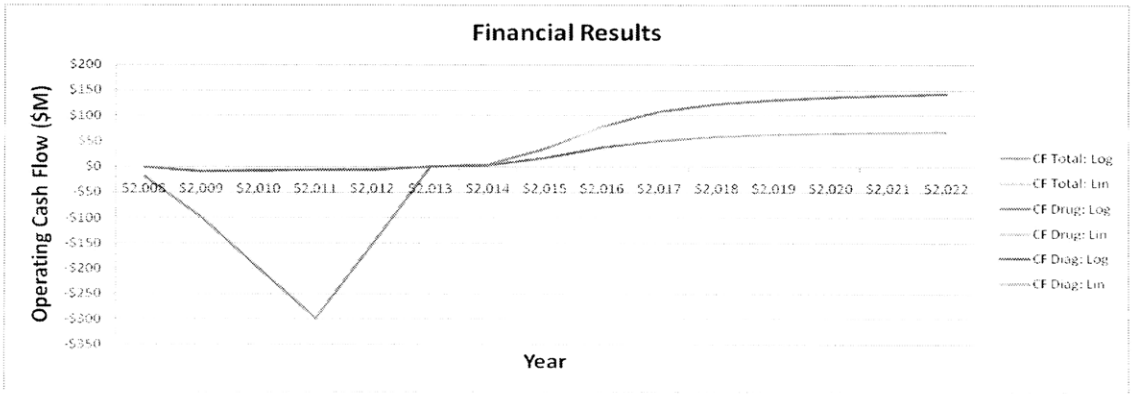

Fig 31: Scenario 1: Operating cash flow (drug and diagnostic)

Scenario 2

A low percentage of responders (20%) and a high percentage of polluters (30.57%) results in a biomarker with high sensitivity (96%), specificity (89.43%) and positive predictive value (98.89%) but lower negative predictive value (69.43%), therefore the high number of false responders. In a situation such as this, there are very few patients that should have received the drug but didn't (<1%), but a significant number of patients who should not have received the drug, but did. With the price point at $10,000, the net present value for the therapeutic in this scenario is $-74.8mn and for the biomarker $100.1mn - a total net present value of $25.2mn.

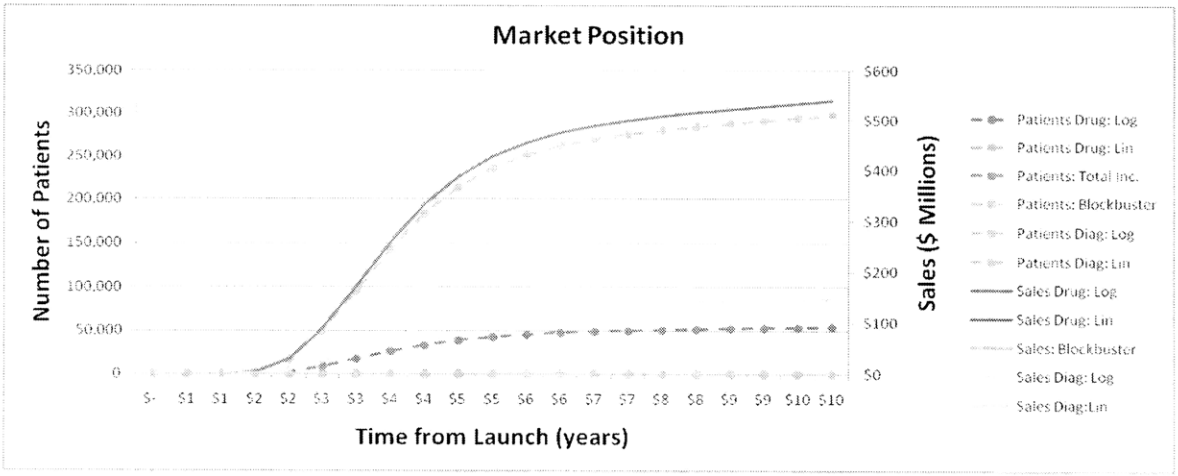

Fig 32: Scenario 2: No. of patients and sales (drug and diagnostic)

The market position chart demonstrates that under this scenario, only approximately 50,000 patients will be on the drug, representing at a price point of $10,000, around $500mn in revenue, and around $280mn in operating cash flow

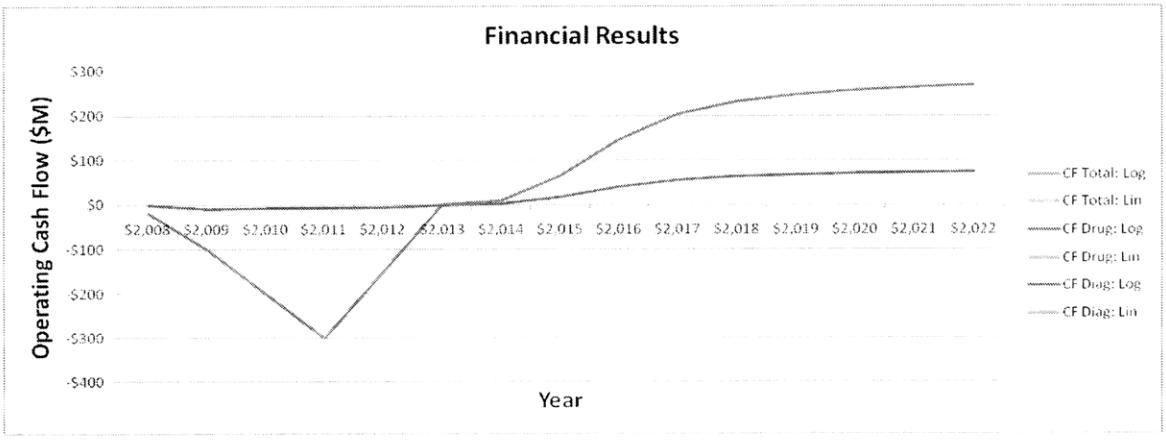

Fig 33: Scenario 2: operating cash flow (drug and diagnostic)

Scenario 3

A high percentage of responders (65%) and a low percentage of polluters (4.8%) results in a biomarker with high sensitivity (95.06%), specificity (91.15%), negative predictive value (95.23%) and positive predictive value (90.85%). A low number of false positives in combination with a large patient population and only 3.2% of responders excluded make this an accurate biomarker. At a price point of $10,000 the net present value of the drug is $518.8mn and the diagnostic $129.8mn giving a total net present value of $648.6mn.

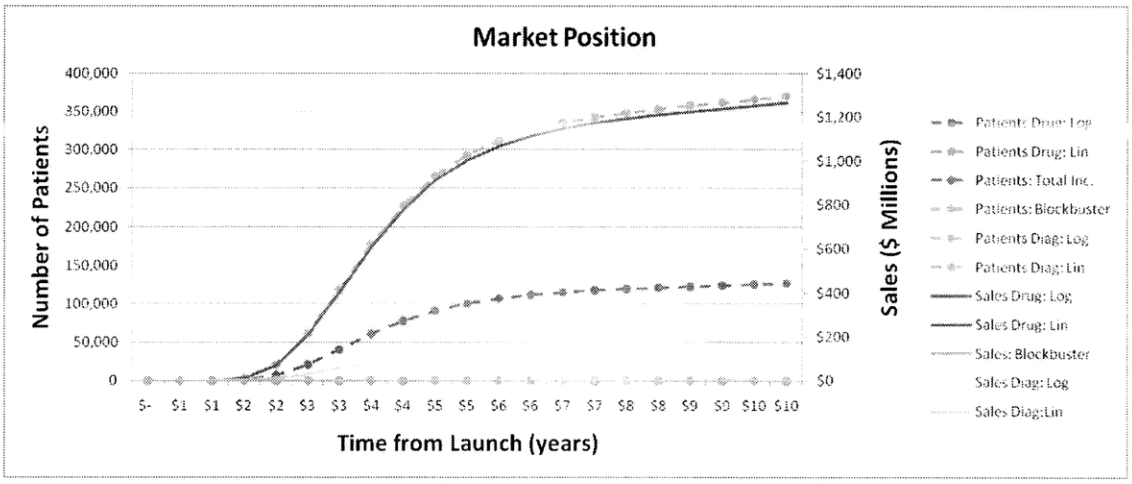

Fig 34: Scenario 3: no. of patients and sales (drug and diagnostic)

The market position chart demonstrates that with these parameters, 10 years from launch around 140,000 people actually end up on drug. At the $10,000 price point, this represents $1.2bn in revenue, and around $400mn in operating cash flow.

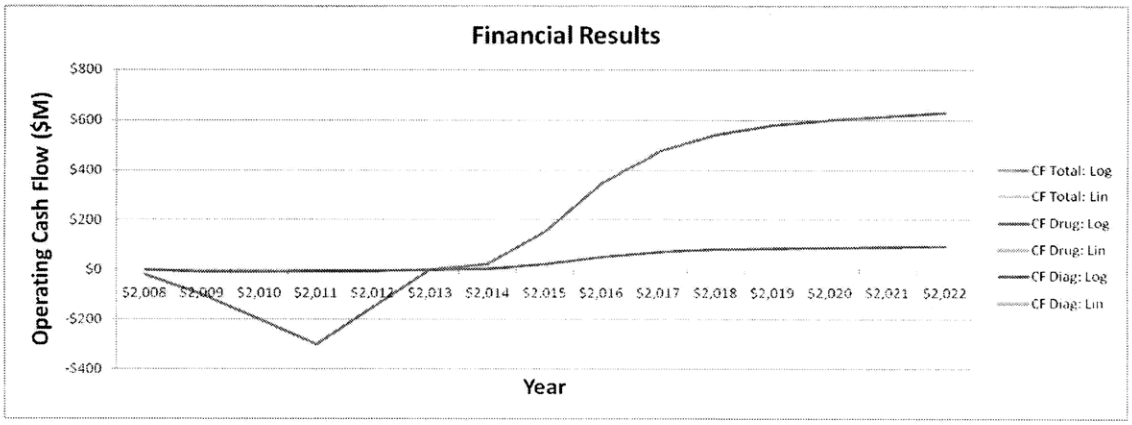

Fig 35: Scenario 3: Operating cash flow (drug and diagnostic)

Scenario 4

A high percentage of responders (65%) and a high percentage of polluters (20.8%) results in a biomarker with high sensitivity (99.84%) and positive predictive value (99.44%) but relatively low specificity (51.94%) and negative predictive value

(79.42%). Although almost all responders are treated, almost half of the non responders (16.8%) who will not benefit from drug, are also captured. At a price point of $10,000 the net present value of the drug is $787.2mn and the diagnostic $143.2mn giving a total net present value (drug and diagnostic) of $930.4mn.

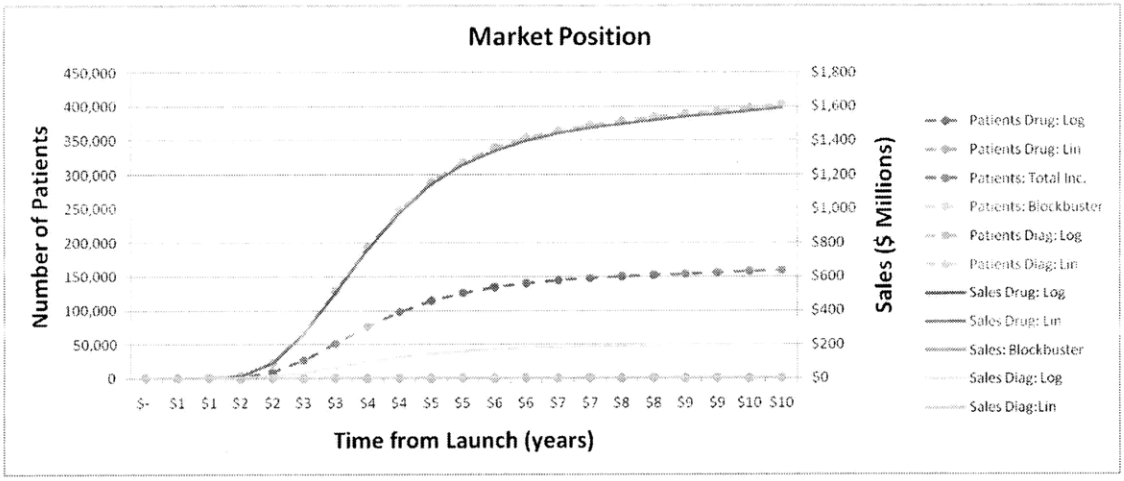

Fig 36: Scenario 4: No. of patients and sales (drug and diagnostic)

The market position chart demonstrates that in this scenario nearly 400,000 people are on drug in year 10. At the $10,000 price point this represents $1.6bn in revenue and approximately $800mn in operating cash flow.

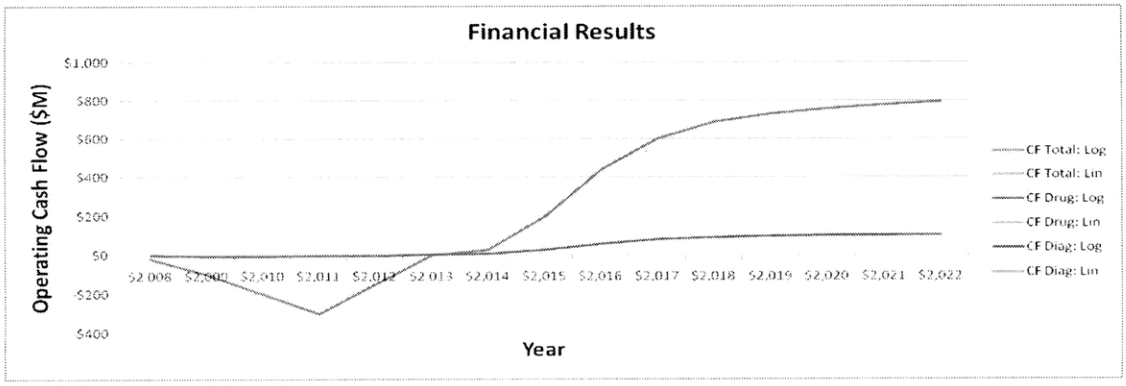

Fig 37: Scenario 4: Operating cash flow (drug and diagnostic)

Scenario 5

A low percentage of responders (20%) and polluters (4.8%) results in an 'accurate' biomarker that it is highly selective for patients that are likely to respond to the given therapeutic (specificity of 99.29%), and the number of 'false positives' or patients who are non-responders but test positive and still receive treatment, is low. With the price point at $30,000, the net present value for the therapeutic in this given scenario is $329.7mn, the biomarker $90.5mn, giving a total net present value of $420.1mn.

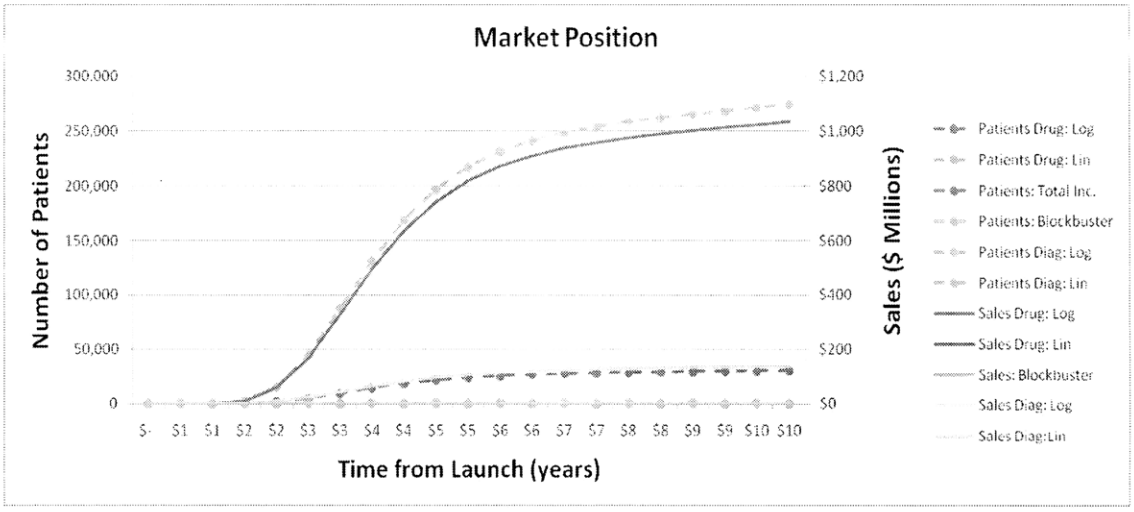

Fig 38: Scenario 5; no. of patients and sales (drug and diagnostic)

The market position chart demonstrates that with these parameters, 10 years from launch only around 30,000 people actually end up on drug. At the $30,000 price point, this represents around $1bn in revenue, and around $500mn in operating cash flow.

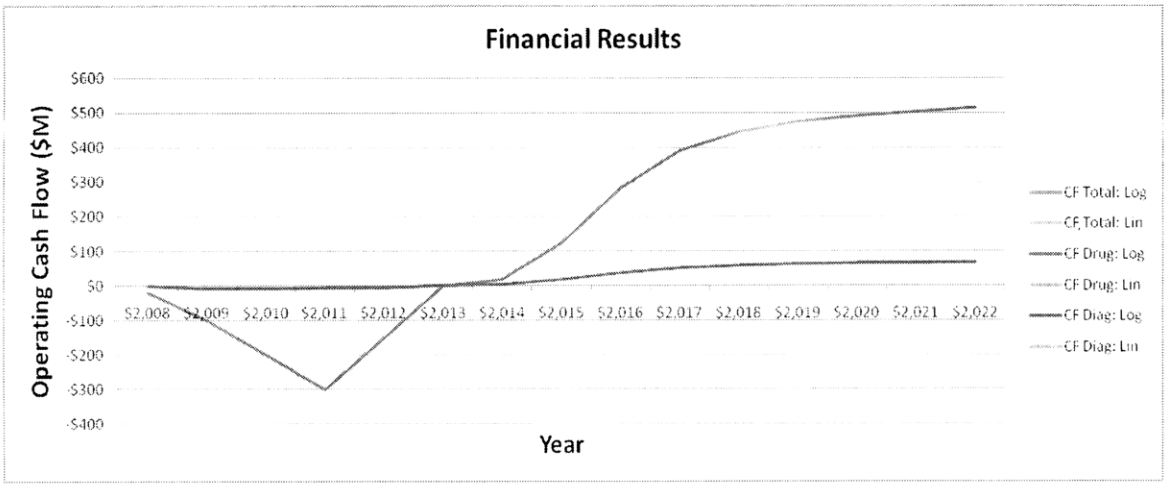

Fig 39: Scenario 5: Operating cash flow (drug and diagnostic)

Scenario 6

A low percentage of responders (20%) and a high percentage of polluters (30.6%) results in a biomarker with high sensitivity (96%), specificity (89.43%) and positive predictive value (98.89%) but lower negative predictive value (69.43%), therefore the high number of false responders. In a situation such as this, there are very few patients that should have received the drug but didn't (<1%), but a significant number of patients who should not have received the drug, but tested positive and did receive drug. With the price point at $30,000, the net present value for the therapeutic in this scenario is $807mn and for the biomarker $100.1mn, giving a total net present value of $907.1mn

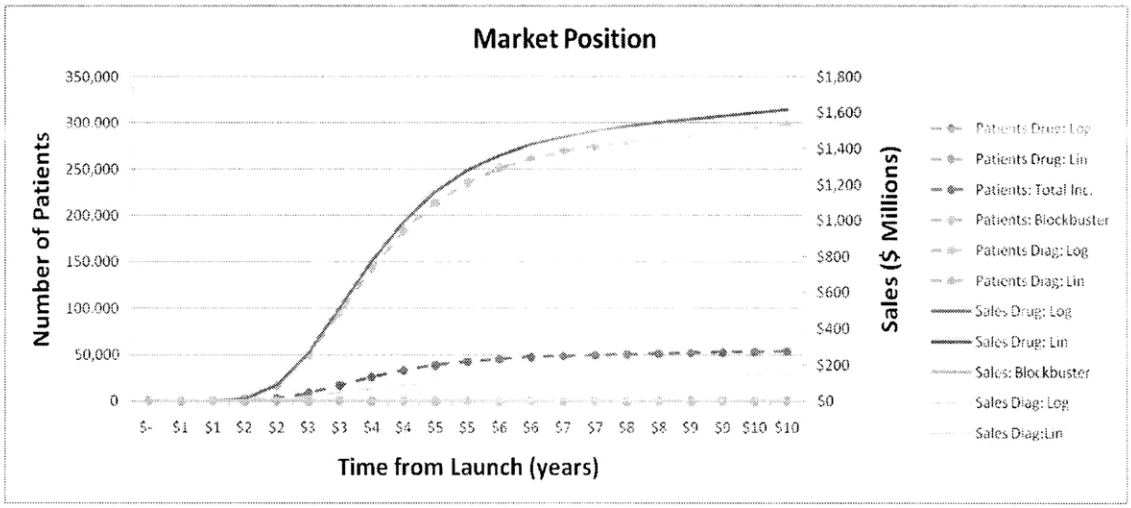

Fig 40: Scenario 6: No. of patients and sales (drug and diagnostic)

The market position chart demonstrates that under this scenario, only approximately 50,000 patients will be on drug, representing at a price point of $30,000, around $1.6bn in revenue, and around $800mn in operating cash flow.

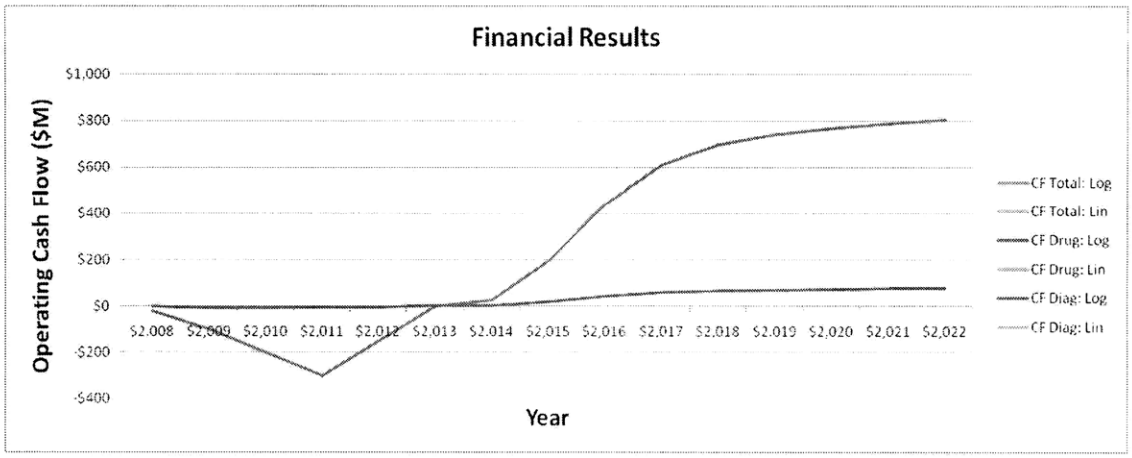

Fig 41: Scenario 6: Operating cash flow (drug and diagnostic)

Scenario 7

A high percentage of responders (65%) and a low percentage of polluters (4.8%) results in a biomarker with high sensitivity (95.06%), specificity (91.15%), negative predictive value (95.23%) and positive predictive value (90.85%). A low number of

false positives in combination with a large patient population and only 3.2% of responders excluded make this an accurate biomarker. At a price point of $30,000 the net present value of the drug is $2587.9mn and the diagnostic $129.8mn giving a total net present value of $2717.7mn.

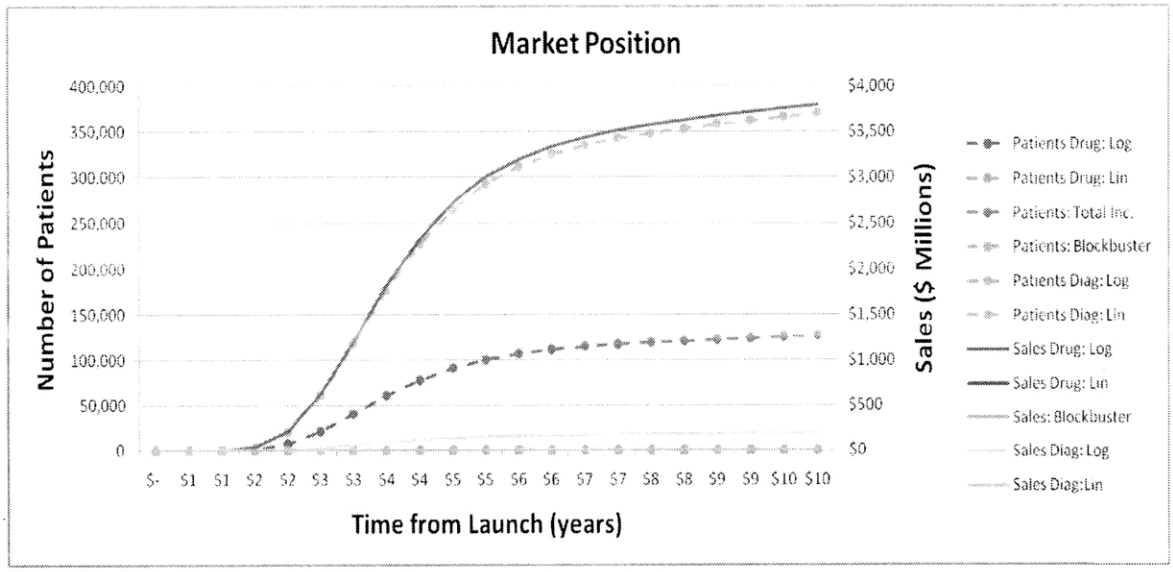

Fig 42: Scenario 7: No. of patients and sales (drug and diagnostic)

The Market position chart demonstrates that with these parameters, 10 years from launch around 140,000 people actually end up on drug. At the $10,000 price point, this represents $3.8bn in revenue, and around $400mn in operating cash flow.

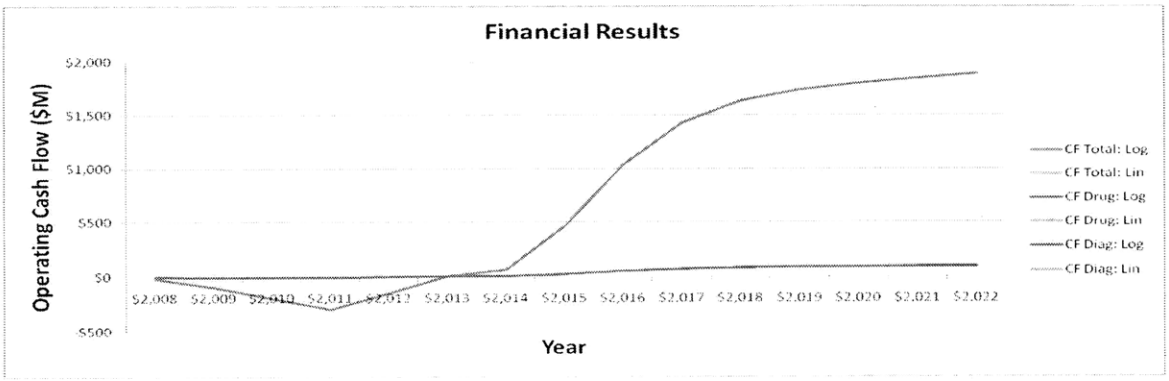

Fig 43: Scenario 7: Operating cash flow (drug and diagnostic)

Scenario 8

A high percentage of responders (65%) and a high percentage of polluters (20.8%) results in a biomarker with high sensitivity (99.84%) and positive predictive value (99.44%) but low specificity (51.94%) and negative predictive value (79.42%). Although almost all responders are treated almost half of the non-responders (16.8%) who will not benefit from drug, are also treated. At a price point of $30,000 the Net Present Value of the drug is $3393mn and the diagnostic $143.2mn giving a total Net Present Value of $3536.1mn.

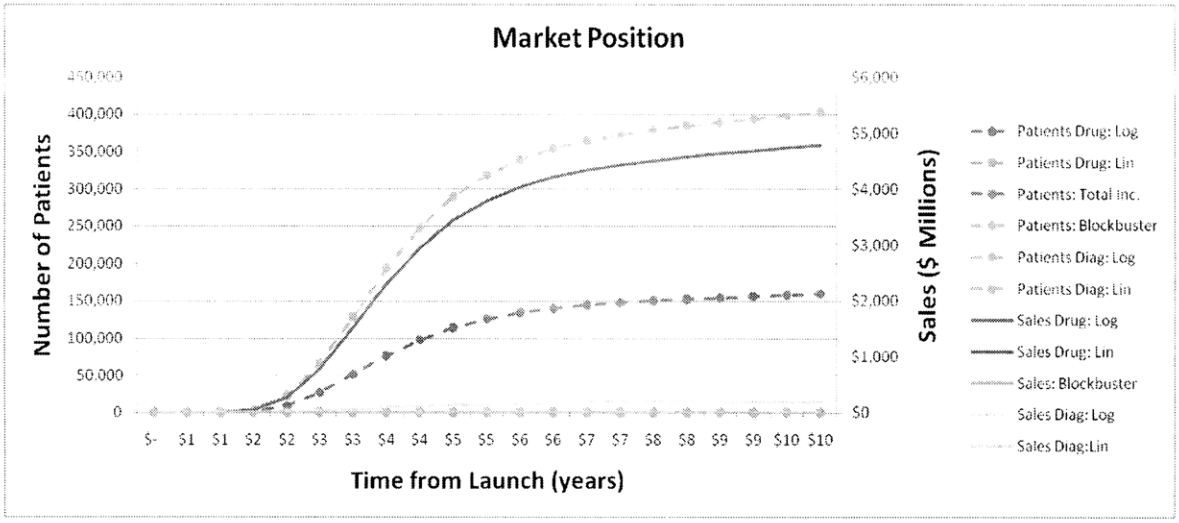

Fig 44: Scenario 8: No. of patients and sales (drug and diagnostic)

The market position chart demonstrates that in this scenario nearly 400,000 people are on drug in year 10. At the $30,000 price point this represents $5.5bn in revenue and approximately $2.4n in operating cash flow.

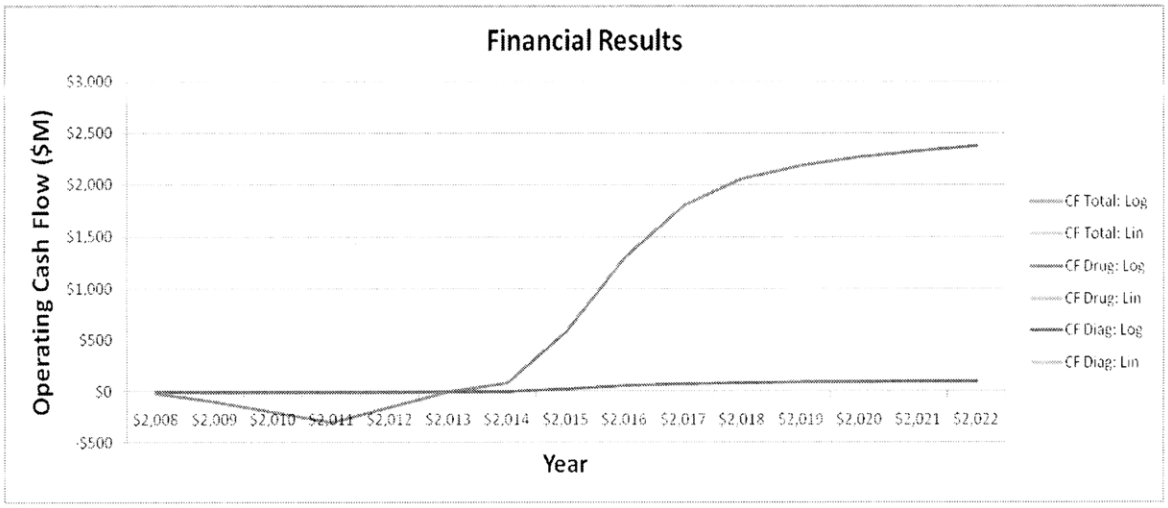

Fig 45: Scenario 8: Operating cash flow (drug and diagnostic)

4.5 Summary of Outcomes of Scenario Modeling

The scenarios modeled in this study span from situations where the percentage of patients who are considered 'responders' to a particular biomarker and therefore candidates for a drug is reasonably low at 20% (scenarios 1,2,5,6) to high at 65% (scenarios 3,4,7,8). The number of 'polluters' or patients who are considered non-responders but are included in the treated pool of patients, ranges from low (scenarios 1,3,5,7) to high (scenarios 2,4,6,8). Price also varies from low ($10,000 in scenarios 1,2,3,4) to high ($30,000 in scenarios 5,6,7,8)

The outcome is that in scenario 1, where the percentage of responders is low, the biomarker is very accurate with few polluters, and the price is low, the net present value of the drug and of the drug/diagnostic combination is very low, and unlikely to be attractive to a pharmaceutical company. In scenario 8, where the percentage of responders is high, the number of polluters is high (and therefore more patients receive drug) and the price is high, the net present value of the drug and of the

drug/diagnostic combination is high, and is therefore likely to be attractive to a pharmaceutical company.

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6	Scenario 7	Scenario 8
Sensitivity (%)	70.89	96.00	95.06	99.84	74.22	96.00	95.06	99.84
Specificity (%)	99.29	89.43	91.15	51.94	99.06	89.43	91.15	51.94
Positive Predictive Value (%)	96.13	69.43	95.23	79.42	95.19	69.43	95.23	79.42
Negative Predictive Value (%)	93.17	98.89	90.85	99.44	93.89	98.89	90.85	99.44

Table 8: Scenario statistical outputs

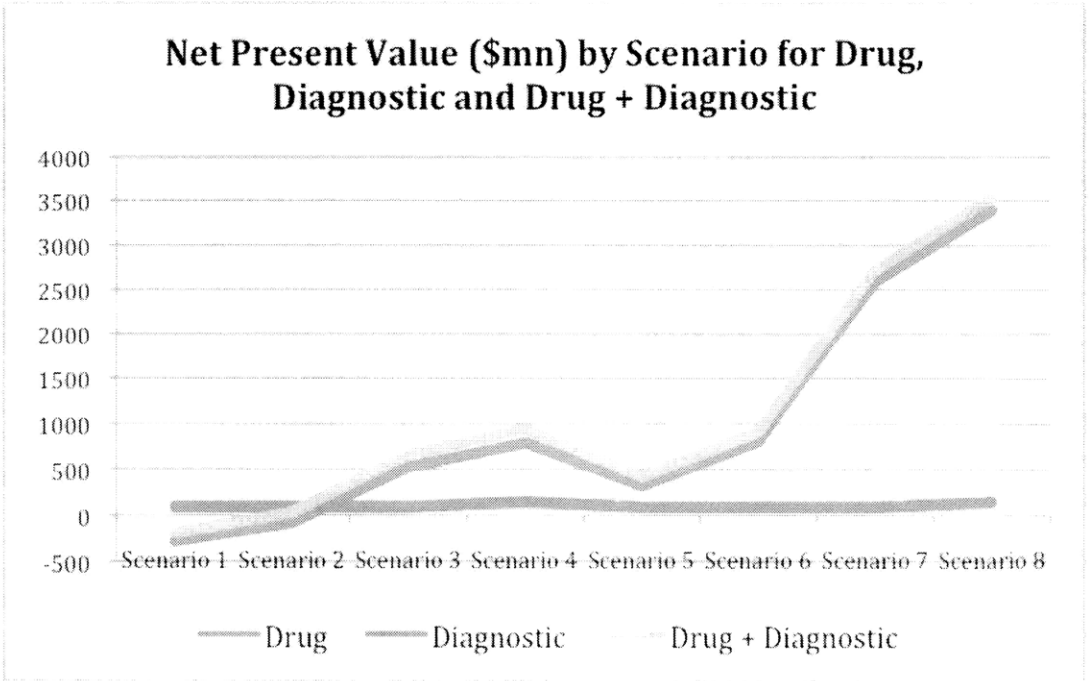

Fig 46: Net present value per scenario

From the perspective of a pharmaceutical company, when considered in the context of today's environment and the increased focus on cost-effectiveness, at a price point of $10,000, only those situations such as scenarios 3 and 4, where an indication contains a large pool of patient responders, does it make sense to 'stratify.' Even if the company is able to charge a significant price premium for a stratified therapeutic it appears from the net present value perspective that there needs to be a 'critical mass' of patients to make it worthwhile. In indications with a smaller number of patients, this could potentially be achieved by developing a biomarker with lower specificities and negative predictive values, and thus a higher number of 'polluters.' who are unlikely to respond to the drug.

This raises a number of ethical challenges. Firstly, in today's environment, most drugs are not stratified and the number of polluters can be very high (it is estimated that only 22.4% of migraine patients are 'pain free' two hours after taking Tylenol[51]). Even for Herceptin, where the Her-2 Neu clinical biomarker should be used to determine potential efficacy, the biomarker is controversial and considered by someto be fairly inaccurate. It is debatable how many patients actually receive the test.[52]

Drugs that have been developed without stratification, or drugs that were stratified as part of a rescue strategy have a large percentage of false responders although this is not necessarily by design. As the industry gets closer to the 'rational design' of stratified drugs, where biomarkers are sought and developed in conjunction with development of the drug, the following tensions arise:

1. Drugs not being developed due to limited patient populations when stratified, despite being effective;
2. Drugs being developed with an associated clinical biomarker that is 'just good enough' as opposed to as specific as possible, resulting in the percentage of polluters driving profitability.

The NPV of the diagnostic alone also demonstrates that the business model for a diagnostic's company will be challenging. Regardless of the scenario, the NPV of the diagnostic component remains low at approximately $100mn. It is likely that this problem will require big pharma to work with, and adequately incentivize diagnostics companies if they choose to pursue stratified medicine.

To summarize, the success of stratified medicine is highly dependent on a number of variables, including pricing and efficacy of both the drug and the biomarker. Furthermore, it is essential to check for the prevalence of the biomarker in the disease population in order to ascertain commercial viability.

In following section of this thesis, through interviews with patient advocacy groups, I analyze whether this is in fact an ethical dilemma, and what the relationship between efficacy and profitability should, and could look like.

5.The patient perspective – ethical considerations in stratified oncology therapeutics

5.1 Summary of interview

The stratification of patient population based on the use of biomarkers raises the potential for scenarios whereby smaller patient populations, which may be exacerbated by the specificity or effectiveness of the biomarker, may adversely affect the economics of the pharmaceutical industry.

In order to explore whether this is an ethical issue, and how patients percieve this may impact the universe of cancer sufferers, in-depth interviews were conducted with senior members of the following five patient advocacy groups:

- Inflammatory Breast Cancer Support Group – a patient advocacy group focused on providing support and advice to patients with inflammatory breast cancer;[34]
- C3 Colorectal Cancer Coalition – a patient advocacy group dedicated to fighting colorectal cancer through patients support and policy change;[35]
- Joan's Legacy: Uniting Against Lung Cancer – A patient advocacy group focusing on increasing awareness of lung cancer and funding innovative research;[36]
- Breast Cancer Action – A patient advocacy group focused on grassroots patient education and advocating for policy change;[37]
- The Prostate Net – a patient advocacy group focused on providing education services to patients suffering with prostate cancer[38]

Prior to each interview, each interviewee was given a brief overview of :

- The definition of stratified medicine as used in this thesis, namely the use of a clinical biomarker to determine whether a drug is likely to be efficacious or result in adverse side effects;
- A definition of a clinical biomarker, using the HER-2 NEU test as an example, and of 'false positives' as patients who respond positively to the clinical biomarker but do not respond to drug; and
- A definition of specificity of a biomarker, namely that the more specific a biomarker, the more accurate and therefore the smaller the population of false positives

The first stage of the interview consisted of the following questions:

1. What is your opinion of the availability of 'stratified medicines' to patients in the current environment?
2. What is your perception of stratified medicines vs. traditional chemotherapeutic agents in terms of
    a. Efficacy
    b. Side effects?
3. Do you think 'stratified medicines are worth 'more' than traditional therapeutics?
4. If so, how much 'more' do you think they are worth and on what does the price premium depend?

After answering these questions interviewees were then given an outline of the findings from the 'scenarios' section of this work, highlighting the finding that highly

specific biomarkers may result in unfavorable economics for the pharmaceutical industry. Less specific biomarkers (that are still sensitive and therefore have a few false negatives) where a larger number of patients test positive will result in higher profitability. It was pointed out that in today's environment many clinical biomarkers do not have a high level of specificity. The following questions were then asked:

1. Do you think there is a tradeoff between efficacy and profitability – If so, is this getting better or worse over time? Do you think stratified medicine will diminish or magnify this tradeoff? Why?
2. What are your opinions regarding the relationship between efficacy and profitability in the drug industry?
3. What are your opinions about the scenarios regarding clinical biomarkers outlined above?
4. What are your opinions about a drug potentially not being developed due to the fact that profitability is limited, despite efficacy?
5. What are your opinions about a large number of 'false responders' or polluters driving profitability?
6. Is this really an ethical dilemma?
7. How should drug companies manage this from a public relations/marketing perspective?
8. How might your patient advocacy group help manage this tradeoff?

5.2 Interview Results and Discussion

The results of the interviews will be discussed under the relevant headings below as a collation of responses from the interviews

What is your opinion of the availability of 'stratified medicines' to patients in the current environment?

From the perspective of availability from a financial standpoint, all participants were broadly in agreement that those drugs that are available are covered by healthcare insurance, although in some cases there were concerns regarding the lifetime limit of policies. This was more of a concern for breast cancer patients who may require drugs such as Herceptin for a number of years, as opposed to lung cancer patients who may use Tarceva for a shorter prior of time.

Credit was also given to patient assistance programs, especially that of Genentech in terms of ensuring that uninsured patients receive drug in a timely manner.

A primary issue was not over access to the medicines, but access to care, and to physicians experienced with the use of stratified medicines in combination with other medications. The difference in care provided in a community setting as opposed to an academic center or big city was described variously as stark and unacceptable.

There was greater concern over the availability of the biomarkers themselves. According to most interviewees, biomarker testing is not required for the use of many stratified drugs, leading to high expectations amongst the patient population that often led to distressing situations for patients who did not respond.

There was also a general consensus that compared to traditional treatment regimens, a paucity of stratified medicines are available, despite the publicity that has accompanied the advent of biologics. Concern was raised over the use of research dollars not bearing fruition.

It was also widely agreed that stratified agents are often portrayed, both by the scientific community and by companies, as a magic bullet with 'fabulous' promise whereas the reality is far from this.

What is your perception of traditional medicines vs. traditional chemotherapeutic agents in term of efficacy and side effects?

Although patients have some bias towards a perception that stratified medicines are both more efficacious and result in fewer side effects, a universal response was that most patients are given stratified medicines in combination with chemotherapy, and thus it is difficult for patients to establish the difference between the two. Interviewees believed that as technology progresses and the use of stratified medicines becomes distinct from chemotherapy, improvements would be seen in both efficacy and side effects. The comments from the previous question were reflected in this question in that stratified medicines have not lived up to their promise. It was mentioned by a number of interviewees that this may be due to the common perception of stratified drugs as 'magic bullet cures' when this is generally not the case, yet the drug is doing what it claims to do, which is often extension of life by a certain period of time.

Do you think stratified medicines are worth 'more' than traditional therapeutics and if so, on what does the premium depend?

There was a general opinion that chemotherapy is not going away. Any product, whether stratified or otherwise, which aids in providing better outcomes through reduced use of traditional chemotherapeutics would be worth more, but various different reasons for this 'premium' were cited.

The first, and most obvious is that if life is extended more than with traditional drugs, this has an obvious value, but its quantification is challenging. If life expectancy is extended by a number of weeks this creates a vastly different scenario than if it is a number of years.

Quality of life was a key consideration and one that was considered to be easier to quantify. The costs of side-effects can be measured and if an economically quantifiable reduction in side effects is determined, this could be used to establish the premium of any given drug.

Several of the interviewees stated at this stage that they are cognizant of the cost of developing such drugs and were surprisingly sanguine about the need for pharmaceutical companies to generate profit. However, they felt, and many lobby for government support and intervention to control the prices of more advanced therapeutics whilst ensuring companies are able to generate positive net present value on their assets.

Do you think there is a tradeoff between efficacy and profitability? – If so, is this getting better or worse over time? Do you think stratified medicine will diminish or magnify this tradeoff? Why?

This set of questions generated the most varied of all responses, and thus it is worth summarizing each response in turn:

Response 1:

This interviewee felt that there is a clear disconnect between various definitions for efficacy. Current standards really only use survival as a measure of success, yet the feeling was that companies were able to exact profits that were in excess of the efficacy of this drug, and that this had been magnified by stratified medicines through the justification of high R&D costs.

This interviewee felt that the FDA has a responsibility to review and define factors that define efficacy including

- Progression of disease
- Sensitivity to drug
- Survival
- Side effects
- Quality of life

The profitability of a drug should be linked to these and other factors, and detached to some degree from being priced according to just survival and R&D budgets.

Response 2

This interviewee felt that if a drug is effective it would be profitable, and that the profitability should be tied to how effective it is. This individual held the view that drug companies were deep down interested in drugs that were very effective and would not compromise on efficacy for the sake of profitability due to the fear of public relations scandals more than for any other reason.

From a financial standpoint, the view was expressed that the tradeoff between efficacy and profitability was improving due to the fact that the cost of genomic research was decreasing. It was also stated that the true situation was potentially being masked as if a drug was extremely expensive to bring to market, development would be discontinued and therefore although companies were not being unfair with drugs that reached market, there may be a number of drugs that should have gotten to market on the basis of efficacy but were discontinued.

Response 3

This respondent held the view that the answer to this question was dependant on the type of cancer, as opposed to the type of company or company motives. The view was that in an industry with relatively few 'home runs' the price for drugs such as Herceptin, which has had significant impact on the treatment of breast cancer, is justified, however the cost of Avastin can be justified in some indications, and not justified in others (not explained). Generally this interviewee held the view that the tradeoff is present and getting worse in some cases and better in others.

Response 4

This respondent definitely felt that there is a tradeoff between efficacy and profitability for the reason that stratified medicines may not be the most effective way to intervene in cancer in the first place. Due to the trend to stratified medicine, the interviewee felt that the tradeoff was being magnified in the current environment.

The main question highlighted the fact that the rates of relapse around current stratified therapies, for example those that target EGF-R, are very high and the logic of just attacking one target is flawed. By using combination therapies, patients are then exposed to the side-effects of both classes of drugs, thus the point of a stratified agent is defeated.

There was also concern over whether drug companies manipulated the use of drugs in the community setting where physician education is less advanced, and felt that many patients who did not need drug still received it.

Response 5

This respondent felt that it was perfectly justified for companies to charge premiums for stratified medicines, but was concerned that many patients who did not need drug still received it, and many of these cases are directly related to the setting of care. The respondent also felt that R&D costs are decreasing yet the price of drug is increasing, and thus felt that the tradeoff between efficacy and

profitability is being magnified to some degree by stratified medicine. The point was made that this is probably more likely due to 'inefficiencies' in the system, relating to aggressive sales-force tactics (patients unnecessarily receiving drug) and shareholder pressure (imbalance between cost and price) than a cynical ploy by companies to maximize profits.

In summary to this question, it can be construed that an overall opinion is that there is a tradeoff of efficacy in favor of profitability and stratified medicine is in some cases magnifying this tradeoff. However there was very little indication of the perception of the pharmaceutical industry as an 'evil giant' intent on price gouging. The need to make profit was universally accepted but shareholder pressure and a high level of inefficiency in the whole process from R&D to sales is also present.

At this stage in the interview, an outline of the findings from the previous section was given and the following questions were asked:

What are your opinions regarding the clinical biomarkers scenarios outlined?

Almost all the respondents recognized that the scenarios outlined were feasible as companies had a responsibility to shareholders. They did not necessarily agree that this was right, but were sanguine about the realities of the situation. All mentioned that as a patient, with potentially limited time to live, one would want the best biomarker possible to enable them to get to the most effective drug.

What do you feel is the correct balance between efficacy and profitability?

This question was structured by asking what an acceptable rate of 'false positives' within the patient population for a clinical biomarker would be going forward. Answers ranged from 10-25%. Most respondents were aware and mentioned the poor specificity of current biomarkers but felt that if pharmaceutical companies had control over the 'parameters' of the biomarker, this was the range to which they should adhere.

What are your opinions about a drug not being developed due to the fact that profitability is limited, despite efficacy?

It was a widely held view amongst interviewees that this was in fact prevalent and that drug companies routinely discontinued development of drugs that could be impactful to patient populations. Again, the general feeling on this was one of resigned acceptance. One interviewee pointed out that developing a drug with limited profitability would not be ethical from the perspective of shareholders.
A majority of the interviewees mentioned the role of government in this equation. Comments ranged from the fact that government should be promoting and focusing resources on wellness as well as treating illness, and that companies should perform the best R&D possible and that government devise a mechanism to fill the funding shortfall that would enable the development of unprofitable drugs. The current role of government organisations such as the NIH was not considered sufficient, and it was stated by more than one respondent that the huge R&D budgets of industry, government and academia are in many cases redundant, and need to be streamlined.

The opinion was also expressed by two interviewees that direct-to-consumer (DTC) marketing in the US was a huge waste and almost unethical in that patients are often not qualified to interpret the information disseminated this way. The money spent on DTC advertising could be redirected and used to alleviate the issue of drugs not being developed due to profitability issues.

What are your opinions regarding a large number of 'false responders' or 'polluters' driving profitability

The immediate response of many of the interviewees is that this is exactly what happens today. Opinions ranged from believing that, to a certain degree, this situation is preferable to not having the drug on the market at all. To one respondent, this was the 'cost of doing business' that companies aren't concerned about this consideration from an ethical viewpoint, as long as people are taking the drug.

It was accepted that the oncology population is hugely heterogeneous, and there will never be one standard when it comes to biomarkers and patient response. Enabling the continuity of drug development and getting drugs to patients were mentioned as two factors which, under the current system, to some degree justified the 'false responders' driving profitability, but the need for an overhaul of 'the system' was repeatedly mentioned.

Is this an ethical dilemma?

Surprisingly, none of the interviewees felt that this was an ethical dilemma in an isolated sense. Responses to this question included the following:

- Narrowing down patient populations through clinical biomarkers is a positive thing but how to get there is the issue. This is where ethical issues arise, not necessarily in the economics as they are currently defined.
- The options are either to revert to developing drugs that are marketed to the entire population but only work in a small percentage, or to move in the direction of stratification. Given that currently oncology still depends on chemotherapy, any move towards stratification is positive. It is a case of balancing the 'good with the bad.'
- This is an ethical issue but also an evolution of science issue. During this period of evolution and a shift towards more advanced and targeted agents, profitability, whether intentionally or unintentionally, is likely to be driven at the cost of patients who form the real life clinical trial.
- This is more than an ethical issue; it is a systems issue and therefore cannot be defined as an ethical problem as it is difficult to determine who is being ethical. It is perfectly acceptable to maximize profits from a patent, but this right also comes with responsibilities to patients.

In summary, although most interviewees appeared troubled to some degree by the fact that 'false positives' may drive profitability, it was not necessarily

viewed as an ethical liability to just the pharmaceutical industry but more as part of a systemic problem where much broader concerns need to be addressed.

What should drug companies do to manage this from a public relations/marketing perspective?

A prevailing view was that direct-to consumer' marketing should be discontinued by companies as a huge waste of resources, with some interviewees also stating that it should be made illegal, as in most European countries. Most felt that companies that are driven by business objectives should also focus on education on health in society. It was mentioned by a number of interviewees that in less well-informed patient groups, drug companies are hated, and that this should be addressed through companies highlighting, and making more accessible their patient assistance programs. It was widely accepted that the employees of drug companies were interested in providing effective therapeutics to patients, but more effort should go into making sure that the right drugs get to the right patients, and in this regard stratification is a positive development.

A key highlighted concern is the way that pharmaceutical companies disseminate information to patients. Examples cited include:

- Drugs, which fail in clinical trials still being touted for meeting secondary endpoints and portraying this as a success.
- DTC advertising often portrays drugs as being far more effective than they are.

- Companies basing the release of information on the Securities and Exchange Commission (SEC)'s requirements for material disclosure as opposed to what might be best for patients. Many respondents mentioned that companies should release information as soon as they get it, as opposed to waiting until they need to. Examples of this include marketed drugs being tested in new indications as this could improve the practice of off-label usage

How might your patient advocacy group manage this tradeoff?

Multiple points were made in response to this question, but the underlying theme was to present patients with 'unvarnished' information to ensure that they were receiving the facts. Patients now have access to a number of resources, which may or may not be accurate, and patient advocacy groups are the arbiters of this information. The reverse also holds true in terms of communicating with drug companies to ensure that the patient viewpoint is taken into account. Specific points mentioned included;

- Working directly with pharmaceutical companies to ensure that the patient perspective is folded into, and included within business objectives whilst serving the patient population;
- Lobby government both to deal with funding shortfalls and supplementing pharmaceutical R&D spending to find a mechanism to get otherwise unprofitable drugs to market;

- Lobby government for regulatory change to improve the quality of information provided to patients.

One point emphasized by most interviewees was the need, particularly in cancer given many patients have limited life expectancy, to keep patients current in terms of news and new developments. In fact, this was viewed by a number of the interviewees as their own ethical obligation to patients.

6.Discussion and Conclusion

Advanced therapeutics such as biologics are now a permanent fixture in the landscape of oncology treatment. Landmark products such as Herceptin and Rituxan have proved to be highly effective and widely used in the management of various cancers. The use of biomarkers is intended to enable physicians to more selectively deploy therapeutics in those patients in whom there is a higher likelihood of success or less probability of failure. It is this process of 'stratification' of patient populations which has raised both the economic and ethical questions explored in this thesis.

One of the most common reasons for resistance to stratifying patient populations, particularly from the marketing groups within industry, has been that the reduced patient populations will reduce the economic viability of a particular product[7]. A counter argument to this claim could be that a therapeutic that is demonstrated to be effective in a subpopulation could command a higher price[7]. However, given the high price of biologics today, which can range from $10,000 to $70,000 per year and cost pressures on the healthcare system, I decided in each of the scenarios to hold prices in line with cost of current therapies.

Another counterargument to the market size claim is that market adoption penetration may increase thus compensating for the loss of market size. However, it appears that gold-standard drugs such as chemotherapeutics are so well established that new, advanced therapeutics may be viewed with suspicion and may take longer to achieve market adoption.[9]

Therefore the first part of this analysis examined, using IMS data. the 'adoption velocity' of stratified therapeutics, compared to gold-standard chemotherapeutics. The analysis found that over the life of a drug, non-stratified therapeutics initially indeed appear to have been more successful and had a higher adoption velocity and therefore rate of market adoption than stratified medicines. However, this analysis contains the limitation that chemotherapeutics have been on the market for much longer than traditional therapeutics, have been approved for many more indications, thus creating an imbalance in the argument.

To further examine the potential reluctance of physicians to adopt the use of stratified therapeutics, I decided to examine the adoption velocities in the first four years of drug life. When looking at the initial stages of drug life, stratified, and non-stratified medicines were remarkably similar, achieving adoption velocities of 19.4% and 19.8% respectively. This allays concerns regarding physician reluctance to adopt new technologies. If current stratified medicines continue to be approved for new indications, as well as new drugs improving on existing technology, this bodes well for the future of stratified medicine from the perspective of treating physicians.

In order to better understand the pressures facing companies from the financial perspective, I conducted three interviews with analysts from Wall-Street, both to examine their understanding and familiarity with stratified medicine, as well as their thoughts on the economics. It was interesting to note their familiarity with stratified medicine, even beyond oncology, and one interviewee even held the view

that future biologics could be difficult to get to market without a companion diagnostic. Roche, Eli Lilly, Johnson & Johnson, Abbot and BMS were considered to be the strongest players in this space.

An interesting and potentially problematic observation was that the market size for any potential clinical biomarker was unlikely to reach beyond $200mn, presenting challenges for the economic justification for developing biomarkers. The need for pharmaceutical companies to arrive at some sort of mechanism to share risk and reward with biomarker/diagnostic companies therefore becomes very important. This issue is reflected in informal discussions with venture capitalists who are interested in the molecular diagnostic space but are challenged by the right time to invest in such companies.

All analysts interviewed were positive on the concept of stratified medicine, but were all too aware of the inherent conflict between R&D and commercial groups at pharmaceutical companies. They did however feel that the performance of drugs such as Herceptin, Rituxan and Gleevec, all of which are considered blockbusters, should alleviate the concerns of commercial groups, and noted the change in the mindset of the commercial group at Eli Lilly, where a significant percentage of drugs under development are now considered 'stratified.'

To investigate further this concern regarding the economic viability of stratified medicine, a model was developed, as part of a broader Center for Biomedical Innovation (CBI) initiative, to examine the impact of clinical biomarkers, on the economics of a drug. This model takes into account a number of parameters,

including biomarker performance (including specificity), population enrichment, adoption rate, market share and pricing to calculate net present value for a drug.

This study specifically assessed the impact of the specificity of the biomarker and the subsequent number of 'false positives' or 'polluters' within a stratified patient population, on the net present value of a drug.

The results of the model demonstrated that in scenarios with a 'low' price and with a very accurate biomarker that was highly specific, the net present value of the drug/diagnostic is very low, and unlikely to meet various internal economic criteria of commercial groups. However, when the price is 'high' and the biomarker is not very specific, thus resulting is a higher number of false responders, the net present value of the drug/diagnostic combination is high and much more likely to be attractive to commercial groups. As can be seen from the analysis, intermediate scenarios in terms of level of polluters and price result in a somewhat linear net present value curve (Page 67 Figure 46, net present value per scenario).

Many of the stratified therapeutics on the market today were developed as the result of 'rescue' strategies. This means that they were unsuccessful in broader trials but were seen to be effective in a subset population (eg. Herceptin was effective in patients overexpressing HER-2-NEU). As the industry moves more towards 'rational design' of drugs and associated biomarkers, this analysis implies that either drugs may not be developed due to unfavorable net present value, or drugs may be developed with a biomarker that is 'just good enough' as opposed to as good as it

can be, with the result that 'polluters' make a significant contribution to, or even drive profitability.

This issue raises clear ethical considerations, and the final part of this thesis takes into account the patient viewpoint, through interviews with patient advocacy groups. The outcome of these interviews was that interviewees were appreciative of the need for pharmeceutical companies to generate profit, but were understandably concerned that drugs may not be developed or that false responders may drive profit. However, this problem was not considered to be an ethical problem in the strict sense. Other issues, such as the government role in R&D, the use of wasteful direct-to-consumer advertising, the discrepancies of community vs. academic care settings, and the unrealistic expectations and potentially misleading marketing of stratified medicines as magic bullets, were all highlighted as interlinked concerns.

Given that the biomarkers for today's stratified medicines have very low specificity, interviewees stated that a false responder rate of up to 20% is acceptable, and that if false responders driving profitability is the only way for a drug to reach market, then this is potentially the 'cost of doing business.'

All respondents were focused on the need to better engage industry and government to portray the patient point of view. Their lack of hostility towards industry, and an apparent willingness to accept that companies have an ethical obligations towards shareholders, should be considered as positive when examined in the context of the development of stratified medicine. It would benefit the pharmaceutical industry to reciprocate this sentiment by managing better the

release of information related to R&D to satisfy patient, as well as Wall-Street concerns. This could potentially fuel a three-way dialogue among patient groups, government and industry to ensure that drugs that may have historically been considered infeasible for development, are at least given a chance to make it to those patients for whom it could save lives.

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Appendix

I.Investment Analyst Questionnnaire

Stratified Medicine Project: Investment Analyst Interview Guide

May, 2008

Introduction

The MIT Center for Biomedical Innovation Stratified Medicine project examines the economic implications of stratified medicine on manufacturers, regulators, clinicians, patients and payers. Stratified medicine changes the incentives for innovation, alters the drug and diagnostic development process, complicates regulatory review and further extends the fragile reimbursement structure. But if all players adapt, patients will reap the benefits of better clinical outcomes, payers will spend less on ineffective treatments and manufacturers will remain economically viable and continue to develop new products.

The questions in this interview are meant to initiate a broad discussion with Equity Research Analysts to identify the critical factors affecting the development and adoption of stratified medicine from the perspective of institutions & shareholder. It is expected that not all questions will be relevant to every analyst and it is hoped that the discussion will raise new issues and questions not initially anticipated. Covering many areas with most analysts will, however, provide a semi-quantitative overview of the numerous perspectives regarding stratified medicine and demonstrate the relative levels of consensus regarding the key factors affecting stratified medicine.

This guide anticipates interview lengths of 30 minutes to 60 minutes. It is incumbent upon the interviewer to monitor the time and depth allotted to any single area to ensure that a reasonable breadth of areas receives attention so that the analyst's broad perspective is represented.

All interviews will be confidential and no attribution to individual interviewees or their company will be disclosed.

This Discussion Guide begins with a brief overview of the stratified medicine project and then contains questions in the following areas which we believe will be of interest to institutional shareholders

Overview of the MIT Stratified Medicine Project

Stratified medicine can provide substantial benefits to certain development programs - in some cases being critical both for regulatory approval and for gaining market acceptance. But applied to programs that do not possess the proper qualities and attributes, stratified medicine might only result in delay, increased cost and smaller markets.

Objectives: CBI's stratified medicine program examines the conditions that favor using stratified medicine approaches. We believe those conditions span from the patient's clinical presentation through

the therapeutic marketplace, ultimately reaching back to the drug development process. Specifically, this project intends to:

- **Discover development and marketing insights** concerning the opportunities and challenges facing a stratified medicine. This will be accomplished by testing and extending previous modeling regarding
  - Clinical development alternatives for both therapeutic and diagnostic
  - Regulatory considerations
  - Physician, patient and payer dynamics
  - Competitor responses and incentives for follow-on products
- **Determine a firm's risk and expected economic performance** if stratified medicines become the predominant product type in a company's portfolio
- **Shape public policy formation** through evidence based analytics regarding the financial and regulatory conditions stratified medicine requires to achieve economic sustainability, therapeutic innovation, healthcare access and public health improvement.

CBI's unique stratified medicine program: The multiple factors that impact stratified medicine occur over many years and across a broad functional span. This presents challenges for their analysis, public policy development and corporate decision making. The program overcomes these challenges by:

- **Employing an inclusive process** that systematically brings together the required expert perspectives
- **Developing quantitative** simulation models which transparently show the interaction of the many factors under a variety of scientific possibilities, regulatory situations, management decisions and marketplace reactions.
- **Analyzing projects and public policy simultaneously** to firmly ground policy in day-to-day reality and ensure that multi-year projects consider broad environmental changes
- **Creating a "safe harbor"** collaboration mechanism for Stakeholders to conduct, share and discuss objective, quantitative analysis in this important area

Industry Trends

- **What, in your opinion, is the definition of 'stratified medicine', also known as personalized medicine or tailored therapeutics?**

- **What examples would you use to demonstrate the financial success of stratified medicine (beyond Herceptin® and Gleevec®)? To demonstrate its clinical failure?**

- **Which, if any stratified medicines have you covered to date, and how have attributed value to it differently, if at all, from other therapeutics and diagnostics?**

- **Which companies do you see at the forefront of 'stratified medicine'?**

- **In 5 year's time, how many therapeutics do you believe will be developed using this approach?**

How has/will Stratified Medicine change life sciences companies' strategies?

- **What are your views on the future of the 'blockbuster drug?'**
- **How do you believe investors view the impact of stratified medicine on market sizes? Do they think that stratified medicines will experience different market penetration, pricing, physician adoption and patient acceptance compared to classic medicines?**
- **Do you believe that stratified medicine will contract or expand a particular market (eg: Breast cancer)?**
- **How do you expect diagnostics companies to benefit from Stratified Medicine?**
- **What changes do you anticipate in commercial strategies?**

Regulatory Role

- **How do you believe that the FDA approval processes will facilitate or impede the approval of stratified medicines that require both a diagnostic and a therapeutic?**
- **Do you believe it would make a difference if the diagnostic is a "home brew" or a "kit"?**
- **How have you seen the FDA and EMEA begin to adapt to stratified medicines?**

Physician Acceptance

- **Do stratified medicines gain faster or slower adoption than classic medicines? What do you feel are the key barriers to physician adoption of a stratified medicine?**

Payer Reactions

- **Do payers perceive stratified medicines as a good value?**
- **Do stratified medicines gain faster and/or more favorable formulary placement?**

Misc

- **Are there any further thoughts you would like to share with us regarding your views?**

II.Patient Advocacy Questionnaire

Graduate Thesis Research – Sameer A Sabir (sameers@mit.edu)

Patient Advocacy Questionnaire: (Oncology) Stratified Medicine

Prior to asking questions, give the interviewee a brief overview of what we mean by stratified medicine. Clarify and emphasise the role of the clinical biomarker – use herceptin as an example. Explain the variability in biomarker sensitivity/specificity

5. What is your opinion of the availability of 'stratified medicines' to patients in the current environment?
6. What is your perception of stratified medicines vs traditional chemotherapeutic agents
    a. Efficacy
    b. Side effects
7. Do you think 'stratified medicines are worth 'more' than traditional therapeutics
8. If so, how much 'more' do you think they are worth and on what does the price premium depend?

Outline findings from the MIT stratified medicine model:

- that with a clinical biomarker with a very tight specificity, the drug is likely to work on most of the patients who test positive, but profitability is low.
- Clinical biomarker is not very specific (but is sensitive), larger number of patients will test positive, and there will be more 'false positives' and higher profitability

9. Do you think there is a tradeoff between efficacy and profitability – is this getting better or worse over time? DO you think SM will diminish or magnify this tradeoff. Why?
10. What are your opinions equation between efficacy and profitability in the drug industry.

11. What are your opinions about the scenarios regarding clinical biomarkers outlined above
12. What are your opinions about a drug potentially not being developed due to the fact that profitability is limited, despite efficacy
13. What are your opinions about a large number of 'false responders' or polluters driving profitability?
14. Where do you feel the correct balance between efficacy and profitability
15. Is this really an ethical dilemma?
16. How should the drug companies manage this from a public relations/marketing perspective
17. How might your patient advocacy group help manage this tradeoff

III. Biomarker Scenario Result Tables

	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6	Scenario 7	Scenario 8
Population distribution								
Percent Responder	20%	20%	0.65	65%	20%	20%	65%	65%
Separation	30	30	30	30	30	30	30	30
Biomarket Cutoff	55	43	44	31	54	43	44	31
Diagnostic Performance								
Sensitivity	70.89%	96.00%	95.06%	99.84%	74.22%	96.00%	95.06%	99.84%
Specificity	99.29%	89.43%	91.15%	51.94%	99.06%	89.43%	91.15%	51.94%
NPV	96.13%	69.43%	95.23%	79.42%	95.19%	69.43%	95.23%	79.42%
PPV	93.17%	98.89%	90.85%	99.44%	93.89%	98.89%	90.85%	99.44%
Price								
Price (drug)	10000	10000	10000	10000	30000	30000	30000	30000
Biomarket population enrichment								
Responder Therapeutic Effect	6	6	6	6	6	6	6	6
Selected Population Effect	5.77	4.17	5.71	4.76	5.71	4.17	5.71	4.76
"All Comers" Efficacy	1.2	1.2	3.9	3.9	1.2	1.2	3.9	3.9
Biomarkers selected %	15%	28%	65%	82%	16%	28%	65%	82%

Table 1: Scenario Statistics

	Selected	Not Selected	Total
Responder	14.2%	5.8%	20.0%
Non-Responder	0.6%	79.4%	80.0%
Total	14.7%	85.3%	100.0%
Polluter Percentage	3.9%		

	Selected	Not Selected	Total
Responder	19.2%	0.8%	20.0%
Non-Responder	8.5%	71.5%	80.0%
Total	27.7%	72.3%	100.0%
Polluter Percent	30.6%		

Scenario 3

	Selected	Not Selected	Total
Responder	61.8%	3.2%	65.0%
Non-Responder	3.1%	31.9%	35.0%
Total	64.9%	35.1%	100.0%
Polluter Percentage	4.8%		

Scenario 4

	Selected	Not Selected	Total
Responder	64.9%	0.1%	65.0%
Non-Responder	16.8%	18.2%	35.0%
Total	81.7%	18.3%	100.0%
Polluter Percent	20.6%		

Scenario 5

	Selected	Not Selected	Total
Responder	14.8%	5.2%	20.0%
Non-Responder	0.7%	79.3%	80.0%
Total	15.6%	84.4%	100.0%
Polluter Percentage	4.8%		

Scenario 6

	Selected	Not Selected	Total
Responder	19.2%	0.8%	20.0%
Non-Responder	8.5%	71.5%	80.0%
Total	27.7%	72.3%	100.0%
Polluter Percent	30.6%		

Scenario 7

	Selected	Not Selected	Total
Responder	61.8%	3.2%	65.0%
Non-Responder	3.1%	31.9%	35.0%
Total	64.9%	35.1%	100.0%
Polluter Percentage	4.8%		

Scenario 8

	Selected	Not Selected	Total
Responder	64.9%	0.1%	65.0%
Non-Responder	16.8%	18.2%	35.0%
Total	81.7%	18.3%	100.0%
Polluter Percent	20.6%		

Table 2: Diagnostic Performance (population basis)

npv ($mn)	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 6	Scenario 7	Scenario 8
drug	-280.6	-74.8	518.8	787.2	329.7	807.0	2587.9	3393.0
diagnostic	89.8	100.1	129.8	143.2	90.5	100.1	129.8	143.2
Total	*-190.8*	*25.3*	*648.6*	*930.4*	*420.1*	*907.1*	*2717.7*	*3536.1*

Table 2: Dcenario financial results (logistic)