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Abstract

Much has been talked about how investing in health care earlier rather than later can be beneficial, from how "biomarkers" offer promise for early disease detection to healthcare system "incentives" that might promote early preventive medicine. Work by health economists has also made clear that the "health capital" of an individual depreciates over time in the absence of "investments" in health. Yet, our current policy makers and healthcare system continue prioritizing care of late-stage complex symptomatic illness, often when cure is impossible and disease reversal is improbable, thus exacerbating public health burden. Critically missing predicates to address this challenge include the following: first, identifying and validating the specific set of presymptomatic biomarkers that will inform the most appropriate intervention timing for those medical conditions amenable for early intervention; second, shifting fundamental health economic incentives to influence the appropriate disease prevention market; and third, formulating and executing a viable economic framework of reimbursement. We examine these predicates and propose actionable policy recommendations that may help align multi-stakeholders to improve the public health.

Keywords Preventive medicine, Health policy, Health economics.

Introduction

It is widely acknowledged that investing in health care earlier rather than later can improve public health and lower healthcare costs. Despite this observation, the US healthcare system continues prioritizing treatment of late-stage complex symptomatic illness with expensive medical interventions, often when disease reversal is improbable. This approach is not cost-effective. Over the last 40 years (1), the US has consistently spent more on health care as a share of the economy than any other country and ranked last, among high-income countries, on access to care, administrative efficiency, equity, and health care outcomes.

Over 50 years ago, Michael Grossman introduced the concept of "health capital" (2), a cornerstone of modern health economics and health policy. This concept views health as a capital asset that yields a return of time lived in good health and that is impacted by social determinants of health such as age, wages, and education. Grossman described the demand for health care as derivative of the more fundamental demand for good health. However, with Grossman's model, the demand for health care is reactive, generally occurring only after observable signs of decreased health capital are evident.

Support to prioritize early disease intervention should not be misinterpreted as an optimistic promise to cure all medical conditions. The cause(s) of many diseases remains poorly understood, and not all medical conditions are yet amenable to effective early disease intervention. Large-scale multidimensional sets of relevant data from both health and disease states will be needed to broaden the application of early disease intervention (3). Nevertheless, early intervention has already offered promising results for those with presymptomatic hematologic malignancies such as high-risk smoldering multiple myeloma (SMM), monogenic diseases such as spinal muscular

atrophy (SMA) certain type of inherited blindness, and presymptomatic complex chronic diseases such as type 1 diabetes mellitus (T1D) (3-8).

Continuous emphasis on social determinants of health (9-11) and preventive medicine initiatives (12, 13) are important but not enough to prioritize the efforts toward effective early disease prevention. Three key elements that need to be addressed include the following: first, updating the Biomarkers, EndpointS, and other Tools (BEST) Resource; second, influencing the appropriate disease prevention market; and third, formulating and executing a viable economic framework of reimbursement. We examine those elements and provide policy recommendations focused on the US context, given that it has the world's largest healthcare market, a thriving biopharmaceutical ecosystem, and regulatory policies with global effect.

Biomarkers

Since 2015, the BEST Resource has been used to inform biomedical research, clinical practice, and the regulation of medical products by the FDA (14). The BEST Resource is a glossary intended to be periodically updated with additional terms and clarifying information. Edits to the BEST glossary could help overcome the challenge in identifying and monitoring presymptomatic high-risk individuals in trajectory from health to symptomatic disease. From a technical viewpoint, early intervention depends on both timely diagnosis and the availability of effective solutions to correct abnormalities or delay their onset. These two predicates are described as follows.

First, in those medical conditions that are amenable for early disease intervention, timely identification of individuals with latent medical conditions will require presymptomatic disease biomarkers. These include traditional "risk biomarkers" to identify the individuals at high risk for developing a disease and new 'pre-diagnostic monitoring biomarkers,' which should be measured

repeatedly over time, on at-risk individuals, to identify those that are indeed in the trajectory from health to disease.

Second, the development of effective solutions to correct abnormalities, before clinical signs and symptoms are manifested, will benefit from using traditional predictive and response biomarkers. The former identifies the individuals that are likely to experience an effect from exposure to a medical product. Response biomarkers may include pharmacodynamic biomarkers as indicators of intended drug activity, surrogate endpoint biomarkers as surrogates for a clinical efficacy endpoint, and safety biomarkers to monitor adverse effects on biology in response to treatment. Time-tested clinical efficacy endpoints measuring observable symptomatic outcomes will continue to be important to the medical practice focused on disease care.

In a study that assessed FDA approvals of drugs in 3 periods, it was reported that surrogate end points were used in 48.3% (1995-1997), 60.3% (2005-2007), and 59.3% (2015-2017) of all new therapeutic agent approvals (15). Certainly, the FDA recognizes that the use of surrogate endpoints may be the only practical way to evaluate the therapies intended to prevent manifestation of symptomatic disease that has a long latency period (14). The agency encourages the development of novel surrogate endpoints through both an investigational new drug (IND) application and the Biomarker Qualification Program.

The traditional approval pathway generally requires “validated” surrogate endpoints. “Validated” surrogates, supported by strong data, have been established to predict clinical benefit. The accelerated approval pathway can rely on surrogate endpoints that are “reasonably likely” to predict clinical benefit. "Reasonably likely" surrogates do not have evidence of validity. Thus, industry sponsors must confirm efficacy in post-market trials. Ideally, surrogate endpoints should

lie along the therapeutic pathway between an early intervention and a clinically meaningful benefit.

To illustrate the two above-mentioned predicates with an example, consider type 1 diabetes mellitus (T1D). The lifetime risk of developing symptomatic T1D approaches 100% once two or more islet autoantibodies are detected in genetically at-risk children (16). With T1D, it is now possible to determine the genetic risk at birth with 'risk biomarkers.' For example, genes include interferon-induced helicase C domain-containing protein 1 (IF1H1), sialic acid acetylesterase (SIAE), and the interferon regulatory factor 7 (IRF7)-driven inflammatory network (IDIN). Later, during childhood (5–7 years), using 'pre-diagnostic monitoring biomarkers,' it is possible to distinguish those presymptomatic individuals already progressing along the disease trajectory. Examples of 'pre-diagnostic monitoring biomarkers' include glutamic acid decarboxylase (GAD) and protein tyrosine phosphatase (ICA512) autoantibodies against pancreatic beta cells (17).

Very recently, on November 17, 2022, using 'surrogate endpoints biomarkers' (stage 2 T1D, asymptomatic dysglycemia), the FDA-approved teplizumab as the first drug ever to delay progression of T1D. Trial results, with patients at risk of developing T1D, showed that 55% of teplizumab-treated patients did not develop the condition, as compared with 28% of placebo-administered patients (5, 8).

Influencing the appropriate disease prevention market

The resulting improvements in public health that may be derived from early disease intervention can create frictions among stakeholders whose revenues depend on supplying goods and services to the disease care market. In particular, some biopharmaceutical companies might be reluctant to shift managerial attention, time, and money to preventive medicine ventures that do not strengthen their market position in presently served disease care markets.

Nevertheless, the biopharma industry has begun to show interest in supporting long-term internal ventures focused on early disease intervention. (18) Examples include Janssen's World Without Disease Accelerator, an intrapreneurial venture focused on delivering commercial solutions for early disease interception; Roche's Personalized Healthcare, a companywide initiative aimed at delivering transformational innovation to cure or prevent disease; and Provention Bio, the developer of the first and only FDA-approved drug to delay the onset of stage 3 T1D. Additionally, life science venture creators, such as Flagship Pioneering, have recently called for a new "Preemptive Medicine and health security"(19) paradigm that prioritizes health investment on interventions to preempt, prevent, or delay disease.

While these industry-led initiatives are important to prioritize early disease intervention, not just late disease care, regulators must avoid supporting the wrong prevention market. For instance, in some cases, encouraged by some players within the biopharmaceutical industry and health systems, multi-center randomized clinical trials (RCTs) have created the wrong prevention market (e.g., for treating high blood pressure, high cholesterol, high blood sugar as soon as the "condition" is detected but before the "disease" is manifested). For all three "conditions," most people will realize roughly as much benefit as harm from taking drugs (20). The early disease intervention approach described in this article is based on a different model. One that recognizes the contribution of interindividual variation to differences in disease susceptibility, disease progression, and response to drugs. This is particularly important with complex diseases where risk biomarkers may be influenced by a combination of causal genetic (single highly penetrant alleles or polygenic risk scores), environmental, and holobiont factors. Informed by the BEST biomarkers, the recommendation is to monitor and stratify subgroups of at-risk presymptomatic

individuals and assess both the therapeutic window and timing of intervention where it is most likely to prevent progression to symptoms.

Economic framework of reimbursement

In the US, with health expenditures at nearly one fifth of total gross domestic product, greater emphasis is needed on value for money. As such, medical interventions should not only be shown to be effective, but also cost-effective. In the context of early disease prevention, cost-effectiveness can be defined as the cost-per-life-year gained, and cost can be defined as the cost of early intervention minus the money saved by the avoidance of routine late-stage disease care (21).

Typically, health insurance programs pool resources and spread the financial risk associated with major medical expenses across the entire population to benefit more people. Broadly speaking, a health insurance risk pool is a group of individuals whose medical costs are combined to calculate premiums. Pooling risks together –cost-sharing– allows the higher costs of late-stage investment in health capital of the less healthy to be offset by the relatively lower costs of the healthy.

Late-stage chronically ill patients tend to incur higher medical costs. They are usually suffering from comorbidities and ineffective poly-pharmacy treatments, taking between two and five drugs each day (22). Yet, society has come to accept an established cost-sharing structure doomed to failure (if not patient bankruptcy) as it keeps patients dependent on an unending stream of expenditures while failing to resolve their underlying health problem.

Consider cancer treatment in our current system of disease care. Once signs and symptoms are manifested, expensive treatment is initiated, short period of remission and relapse follows treatment, and later, ultimately, the cancer becomes refractory to any therapy.

In many cases, late-stage treatment enables longer progression-free survival and more durable responses, thus providing symptomatic benefit. However, early disease intervention, when

effective, could protect health systems from expensive medical interventions including high-priced hospitalizations and costly treatments that only provide temporary remission for end-stage disease. In this case, at-risk presymptomatic individuals with no end-organ damage represent higher risk than non-risk individuals with larger stock of health capital. However, their medical and financial risk would potentially be lower than those of late-stage chronically ill patients.

The transition toward early disease intervention, however, would require cost-sharing agreements across payers who, in healthcare economies like that of the United States, are subject to shifting risk pools as policyholders move across payers based on employment or health enrollment status. This is known as the "patient churn," and it may disincentivize insures from making investments in potentially transformational early disease interventions.

Implications for policy

Grossman's health capital theory has had a large impact on healthcare. However, Grossman's model needs to be updated. Over 50 years after its introduction, public health policy has not contributed enough to the delivery of improved health outcomes via early prevention medicine. Feasible and reliable presymptomatic biomarkers are required to identify, monitor, stratify, and intervene high-risk individuals that are in trajectory from health to irreversible symptomatic disease.

As noted earlier, the FDA has shown substantial support for the validation of new biomarkers and surrogate endpoints through the Biomarker Qualification Program (14, 15, 23). Most recently, the 2022 Public Law 117-103 was enacted to create the Advanced Research Projects Agency for Health (ARPA-H) in the US for funding bold biomedical research to prevent, treat, and cure the diseases. Despite these advances, ongoing challenges must be overcome to further promote biomarker development. Biomarker-defined subgroups of at-risk presymptomatic individuals

represent a smaller market for industry sponsors. Thus, it will be necessary strong incentives for investors, small entrepreneurial biotech companies, and large established drug developers. Beyond the accelerated approval pathway that can rely on surrogate endpoints, other FDA regulatory designations exist, such as the Fast Track, Breakthrough Therapy, and Priority Review designations.

Early approval pathways are intended to strike a compromise between access to promising therapies today and confirmatory evidence tomorrow (24). To keep the early disease invention market free of worthless or hazardous medical products, biomarkers' evidentiary standards must be upheld as identified in the FDA's Critical Path Initiative (14).

Legislators would likely need to mandate cost-sharing policies that adequately address the "patient churn" issue. New regulation will be needed requiring all insurance companies to assume the remaining debt obligations of new policyholders who are switching plans. Two approaches may overcome this hurdle: first, the National Association of Insurance Commissioners (NAIC) may provide some degree of uniformity of regulation from state to state. In the past, NAIC has drafted and adopted amendments (25) to model laws such as the Health Carrier Prescription Drug Benefit Management Model Act to address the issues related to transparency, accuracy, and disclosure regarding prescription drug formularies and discriminatory benefit design. However, these models are not enforced by law and have no effect unless they are adopted by a state. Second, Congress will need to enact federal statutes to enable uniformity. This has been done in the past. For instance, with the Patient Protection and Affordable Care Act of 2010, federal laws created uniformity in partnership with the existing state-based system.

Although the challenges faced to implement an effective early disease intervention approach may seem staggering, much can be done to stem the burdens imposed by late-stage disease care through

proactive incentives and policy recommendations such those described here. If that is the case, in a few years, health systems will prioritize early disease intervention. Then, medical care will be an intermediate demand derived from the demand for preserving good health, even before there are observable signs of decreased health capital that leads to irreversible disease.

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Conflicts of interests

No competing interests.

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