

Improving the Translational Pathway for Genetic Tests:

Addressing the Challenge of Evidence Gaps

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This draft problem statement represents the ongoing work of the Center for Genomics and Healthcare Equality (CGHE) and is offered as part of the background materials for the Workshop: Integrating Molecular Diagnostics into Health Care, Oct. 29-31, 2007.

The authors invite your feedback as part of the workshop discussion to:

- 1. debate the merits of the arguments presented below**
- 2. ensure the accuracy and usefulness of the graphic depiction of the translational framework for genetic tests**
- 3. develop policy solutions to address the evidence gaps**

“Where funds are required to generate potential truth in biomedicine, and where the allocation of such funds depends inescapably upon the calculation of financial return, commercial investment shapes the very direction, organization, problem space, and the solution effects of biomedicine and the basic biology that supports it”

Rose, Nikolas, *The Politics of Life Itself*, Princeton Press, 2007, pp 32-33

The promised benefit of the \$3 billion investment in the human genome project was a quantum leap in our understanding the genetic basis of common diseases and in our ability to translate this knowledge into new prevention and treatment strategies.¹ While there are approximately 1000 genetic tests on the market,² they are primarily for rare, single gene disorders and their development largely predates recent scientific advances in genomics, proteomics and enabling technology platforms. Although this group of tests represents important tools for prenatal testing, newborn screening and the field of medical genetics generally, their policy history is unlikely to define or predict the clinical integration challenges facing the new generation of molecular biomarker assays flowing from sequencing the human genome.

These new assays form the technical foundation for the emerging use of genetic susceptibility tests to guide prevention and clinical management, an approach often referred to as “personalized medicine”. Personalized medicine is a phrase that is typically used as shorthand to characterize the broader clinical goal of ensuring the “right diagnosis and treatment, the first time and every time” for each consumer, through the use of molecular biomarkers to characterize individual susceptibilities and metabolism.³ Recognizing that personalized care is based on many factors beyond molecular tests, including a clinician’s knowledge of the patient’s life circumstances, values and preferences,⁴ we use the more specific term “genomic medicine” to refer to the practice of using information derived from genetic testing for risk stratification and tailoring health care interventions to the individual.

We conclude that without significant changes to the regulatory and technology assessment environments in the U.S. for this new generation of genetic tests, these tests will diffuse into clinical practice slowly and haphazardly.⁵ At best, there will be predictable delays in achieving the population-level health benefits of genomic medicine. At worst, patients will be harmed by the use of poorly characterized tests that lead to flawed treatment recommendations. Conceptually, the translational pathway for genetic tests starts with basic research to establish the genetic contribution to disease and culminates in improved public health through the appropriate use of genetic tests in clinical practice. However, gaps occur at various junctures along the pathway in evidence that would support rational decision-making by various stakeholders such as patients, providers and payers. These evidence gaps are the result of a complex set of barriers and incentives that shape the current translational framework for genetic tests. Given the anticipated wave of new genetic tests, there is a growing recognition that now is the time for deliberative policy actions that will increase the likelihood that the benefits of genetic testing outweigh the harms.

Traditional vs. New Genetic Tests

Genomic medicine aims to achieve improved health outcomes by helping physicians and individuals choose the disease prevention and management approaches likely to work best in the context of an individual's genetic and environmental profile.⁶ The promise and excitement surrounding genomic medicine is the potential for genetics to improve population health, a possibility that has gained momentum from numerous federal

initiatives designed to promote the translation of genetic discoveries into clinical applications.^{7,8,9,10} The private sector has also invested heavily in research and development of new genetic-based technologies, based on the belief that tailoring health care to the individual will lead to major improvements in health care quality and efficiency that will be rewarded in the marketplace.¹¹

Examples of this new wave of genetic tests include pharmacogenetic testing (testing to predict an individual's response to one or more drugs) to guide prescribing decisions, and disease predisposition testing (testing to identify future health risks in asymptomatic individuals) that would lead to a tailored prevention strategy. These tests are differentiated from many traditional genetic tests such as carrier testing, (to determine whether an individual carries a mutation associated with a recessive disease) and prenatal testing (to provide information about genetic conditions or birth defects) in several respects. Firstly, they are intended to be used by generalists such as primary care physicians who may be less familiar with the science of genetics and the art of risk communication. Second, these new tests have the potential to be used by large numbers of patients. Third, they have the potential to add substantial weight to current efforts to shift the medical practice paradigm from managing disease complications to preventing or delaying disease onset. All of these applications raise concerns about rising health care expenditures, particularly since several of the earliest examples of genomic medicine technologies have high unit prices and appear likely to increase total costs, while arguably being cost-effective. Finally, what further distinguishes this new group of tests

from traditional genetic tests is an increasing shift toward improving the health outcome of the individual, rather than to simply communicate risk information.¹²

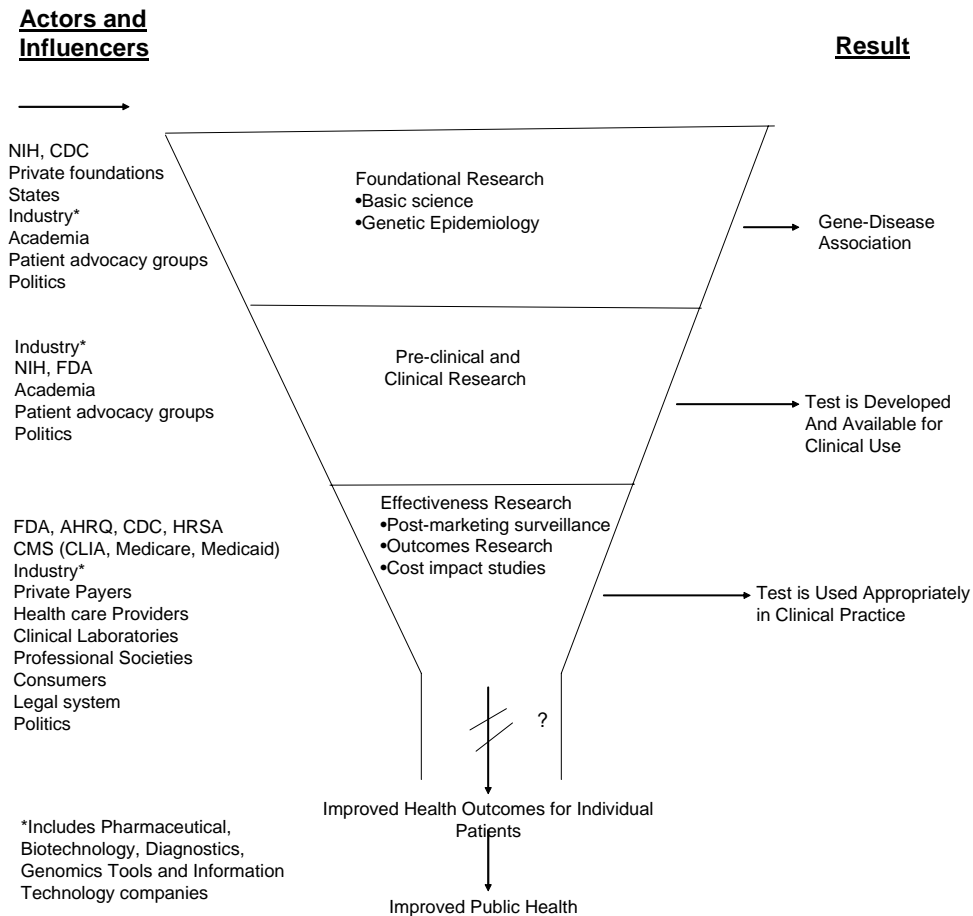
Similarly, there is an expectation that claims of transforming the health care system to one that is more predictive, personalized, pre-emptive and participatory⁷ based in large part on these new genetic tests, will be based on evidence of improved health outcomes with test use. While it is not possible (or desirable) to hold all genetic tests to this higher evidence requirement, our assertion is that it is appropriate to require robust evidence of clinical utility for genetic tests whose stated purpose is to guide patient management decisions.¹³ Indeed, proof of clinical utility (evidence that use of the test leads to improved health outcomes) is the very evidence most desired by clinicians, payers and patients to make informed choices about whether a new genetic test has value or merits coverage.¹⁴ The need for such evidence is particularly acute for tests that 1.) target a prevalent condition, or 2.) have the potential to lead to substantial harm if the test is inaccurate, or 3.) have the potential to result in treatment recommendations with substantial patient benefit. An example of such a test would be one of the new gene expression profiling tests for breast cancer patients that lead to a decision to either forego or accept adjuvant chemotherapy (with the expectation that targeted use of chemotherapy has the potential to extend survival in a subset of women with breast cancer).

Translational Pathway

As illustrated in Figure 1 (see next page), we view the existing translational pathway for new genetic tests as essentially an “information funnel” that starts with basic research at the top of the funnel, leading to pre-clinical and clinical research in the middle part of the funnel, and culminating in effectiveness research at the bottom of the funnel. Each of the three categories of research are separated by a horizontal line that essentially acts as an information filter – new evidence is required before progressing to the next lower level of the funnel. The information that flows through the funnel should drive appropriate use in clinical practice in a way that improves health outcomes for individual patients and ultimately public health. However, the current process of evidence generation is primarily market-driven, with very few requirements for what evidence passes to the next level and what is discarded or used for “no-go” decisions.

At each level of the funnel, a variety of stakeholders can influence the process in a way that leads to certain intended results that represent major translational milestones from bench, to bedside, to clinical practice. There are many groups that influence the process of information generation along the pathway; the groups listed are primarily illustrative and not intended to be comprehensive. Nonetheless, it is clear that the process is complicated by a wide range of actors and influencers with differing agendas and goals. An important early step in promoting effective translation is to identify key stakeholders that need to be involved in any policy initiatives designed to change the current process.

Figure 1: Translational Pathway is an Information Funnel



Of note, the funnel has very steep sides - intending to show that the evidence base for genetic tests narrows rapidly. While there are no financial data regarding the amount of money spent on genetics research specifically, it is well known that funding (both public and private sources) for health services research is dramatically lower as compared to funding for either basic or clinical research.¹⁵ Even for branded pharmaceuticals where we have substantial amounts of clinical data at launch, we have very little data on comparative effectiveness in real-world settings.¹⁶ Therefore, it is entirely predictable that there is very little evidence to demonstrate the clinical benefit of a new genetic test,

since this information is lacking for medical innovations in general. Specifically, there is no direct evidence of a link between test use and improved health outcomes for any of the new genetic tests coming to market within the past 5 years. Under the current translational framework most genetic tests enter clinical practice without first undergoing review and approval by the Food and Drug Administration (FDA). As the vast majority of genetic tests reach the market by way of the laboratory-developed pathway, tests often suffer from incomplete evidence of analytic and clinical validity and with claims strongly influenced by developers' often unproven assertions of potential benefit.

Even if pre-market review of all new genetic tests by the FDA were mandated, there is no existing regulatory requirement for a developer to provide evidence of clinical utility, outside of the narrow setting of drug-diagnostic combination products. Therefore, when comparing the evidence required for marketing a new genetic test with the information needed to make an informed treatment or purchasing decision, it is clear that there is an information gap that is unlikely to be bridged without changes in the current translational pathway.

Of critical importance is the need to increase the awareness of researchers and developers of the information needs and real-world constraints of the end-user communities. A second and equally important message is the need to redesign the research enterprise to produce the desired information regarding both clinical utility and cost-effectiveness over time. In considering different policy options, our immediate goal should be to recommend policy changes that better connect these two ends of the translational

spectrum, so that scarce resources can be focused on answering the most critical questions governing how genetic tests are integrated into clinical practice. The longer-term goal should be to facilitate translation of genetic tests in a way that optimizes the benefits of genomic medicine for all segments of the US population.

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