

The Evidence Dilemma In Genomic Medicine

We need a roadmap for the appropriate integration of genomic discoveries into clinical practice.

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ABSTRACT: An ongoing dilemma in genomic medicine is balancing the need for scientific innovation with appropriate evidence thresholds for moving technology into practice. The current low threshold allows unsubstantiated technologies to enter into practice, with the potential to overwhelm the health system. Alternatively, establishing an excessively high threshold for evidence could slow the integration of genomics into practice and present disincentives for investing in research and development. Also, variable coverage and reimbursement policies can lead to differential access to technology, exacerbating health disparities. There is an urgent need for a collaborative process for appropriate transition of genomic discoveries from research to practice. [*Health Affairs* 27, no. 6 (2008): 1600–1611; 10.1377/hlthaff.27.6.1600]

WITH ACCELERATING DISCOVERIES about the human genome and its role in health and disease, expectations of a new era of personalized health care and disease prevention are mounting. Several years after the completion of the Human Genome Project, genomewide association studies are uncovering genetic risk factors for common diseases of public health significance.¹ Genomic technology has also allowed the sequencing of the entire genome of selected individuals.² The stage is set for an accelerated pace of integration of genomics into medicine, as predicted.³

Undoubtedly, major progress will continue in technology development and our understanding of genetic variations, their interactions, and products.⁴ The number of genetic tests used in clinical practice will increase.⁵ Unfortunately, there is a mismatch between reality and expectation, related to both the quantity and the quality of evidence for genomic medicine. For example, the discovery of variants

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in a gene related to coronary heart disease in 2007 led to rapid commercial plans for moving the discovery into clinical practice.⁶ A similar story occurred in 2006 with the discovery of a genetic variant related to type 2 diabetes.⁷ Genetic risk factors with weak or modest effects have limited added value in predicting and preventing common diseases unless specific effective interventions can be offered based on the information.⁸

We review here the current dilemma of genomic medicine that balances scientific and technical innovation with an appropriate threshold for moving promising technology from research to practice. Our fundamental thesis is that genomics is no different from any other scientific field except perhaps in the sheer volume of new information and technology expected to hit the health care market, and the fact that such information often has implications for the families of those who are tested. Although genomic medicine has been slow in adopting the principles of evidence-based medicine, it still needs to follow the principles of comparative effectiveness.⁹ We argue for a balanced and realistic approach to move such technology from research to practice.

Setting the evidence threshold too high could keep genomics from clinical practice for years. It could also be a disincentive for investments in research and development. On the other hand, an undefined or excessively low threshold could encourage innovations that provide poor value and prematurely move technologies with unsubstantiated claims toward medical practice, with adverse consequences for the health system and its patients. Also, variable coverage and reimbursement policies lead to differential access to technology, potentially exacerbating health disparities.

Where should the line be drawn between research and practice on the basis of evidence? We do not believe that a “one size fits all” threshold for evidence can be developed for all genomic applications; however, there is an urgent need for collaboration to make appropriate transitions from research to clinical practice as part of a rational roadmap for genomic medicine. Although none of the ideas presented here is novel, we aim to explicitly connect the stages of translation of genomics technology from research to practice to the thresholds of evidence needed for moving from one stage to another. We also offer realistic approaches to address these transitions.¹⁰

Pharmacogenomics And Other Genomic Applications: Premature Expectations?

Although pharmacogenomics holds great promise for medicine, it is fraught with development and implementation difficulties.¹¹ For example, cytochrome P450 (CYP450—one of the enzymes responsible for metabolizing numerous drugs) testing is clinically available for assessing genetic variants to help providers prescribe selective serotonin reuptake inhibitors (SSRIs) to treat depression.¹² The rationale is that people who are “slow” metabolizers may have excessive side

effects from medications, whereas “rapid” metabolizers may need a higher dosage for optimal response. The availability of this test is poised to usher in a new era of pharmacogenomics and its potential integration into clinical practice. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, a nonfederal independent multidisciplinary panel established by the Centers for Disease Control and Prevention (CDC) to provide evidence-based guidelines in the evaluation of genomic applications in practice, commissioned a systematic review of the evidence in this area.¹³ The researchers reviewed the evidence regarding whether testing for CYP450 variants led to improved outcomes, and whether test results were useful in decision making. The evidence showed that data on the association between CYP450 variants and the metabolism, effectiveness, and tolerability of SSRIs were mainly derived from heterogeneous studies with small samples. There were no available data on whether CYP450 testing of adults entering SSRI treatment leads to improved clinical outcomes or is useful in decision making. These findings prompted the EGAPP Working Group to issue its recommendation of “insufficient evidence” for the integration of this test into routine practice, discouraging its use until further research can close the evidence gap.¹⁴

This example highlights the current difficulties in pharmacogenomics. Many challenges face pharmacogenomic testing, including limited genotype-phenotype correlations, insufficient analysis of only one or a few genetic variants, complex gene-environment interactions, and the limited correlation between variation in a drug’s blood level and its potential effectiveness as a therapeutic agent.¹⁵ Interestingly, the CYP450 test was cleared by the Food and Drug Administration (FDA) in 2005. This is not inconsistent with the EGAPP analysis above. As the Health and Human Services (HHS) Secretary’s Advisory Committee on Genetics, Health, and Society’s (SACGHS’s) oversight report noted, the FDA plays a role in assessing the clinical validity of genetic tests insofar as it is charged with assessing “safety and effectiveness.” Its evaluation of clinical performance depends on the nature of the test, its intended use, and the amount of existing information about the associations of genetic markers and clinical diagnosis. Prospective data of a test’s clinical validity, however, are often unavailable or incomplete for years after a test is developed, especially for predictive or presymptomatic tests.¹⁶ The FDA only requires demonstration of plausible utility. Therefore, such evaluations of clinical validity and utility require longer-term data not available in any practical sense at the time of initial review.

Over the past six years, the U.S. Preventive Services Task Force (USPSTF) examined only two genetic topics: BRCA1 testing in breast and ovarian cancer, and screening for HFE mutations to identify those at risk for iron overload (hereditary hemochromatosis) in the general population.¹⁷ These two topics were chosen about ten years after the genes for BRCA1 and hemochromatosis were discovered in 1994 and 1996, respectively. In the case of BRCA1, many years after such tests

had begun to make their way into clinical practice, the USPSTF found sufficient evidence for a subset of women with the appropriate family history for referral to genetic counseling for decision making about the possible use of the tests. In contrast, in the case of HFE testing, little wide-scale testing had occurred, and, indeed, the USPSTF found sufficient evidence to recommend against screening in the general population. USPSTF decision making for these tests was impeded by the slow accumulation of scientific evidence on the tests' clinical utility. The paucity of high-quality studies has contributed to the absence of evidence-based practice guidelines and to the differential uptake and reimbursement of these testing technologies in practice.

Developing And Evaluating The Evidence: The Translational Research Process

■ **Translation phases.** We recently described a translation process for genomic medicine that includes multidisciplinary research in four phases revolving around the development of evidence-based guidelines.¹⁸ Phase 1 translation (T1) research seeks to move a basic genome-based discovery into a candidate health application (for example, genetic test/intervention or drug therapy). As the examples above illustrate, the T1 research phase could be shortened considerably by moving quickly from gene discovery to the development of a test that predicts predisposition for heart disease or diabetes. However, a current major challenge is phase 2 translation (T2) research, which assesses the validity and utility of a developed genomic application (for example, a predictive or pharmacogenomics test) for health practice and leads to the development of evidence-based guidelines on the use of a test in practice. Phase 3 translation (T3) research attempts to move evidence-based guidelines into health practice through delivery, dissemination, and diffusion research. Finally, phase 4 translation (T4) research seeks to evaluate the “real-world” health outcomes of a genomic application in practice. The translation research pathway for therapeutics is relatively systematic and understandable, using clinical trials. However, the pathway is less clear for genetic tests and biomarkers in general, especially because most genetic tests are still laboratory developed tests (LDTs) and, therefore, not generally regulated by the FDA. This is the main focus of our discussion.¹⁹

■ **Role of advisory groups.** Government advisory groups have called for more thorough evaluation of tests and development of evidence-based guidelines for their use. In 1997, the National Institutes of Health–Department of Energy (NIH-DOE) Task Force on Genetic Testing first outlined a strategy for assessment of genetic tests based on three components: analytic validity (how well a test measures what it is designed to measure), clinical validity (how well it reflects the phenotype or clinical state it is intended to measure), and clinical utility (whether it broadly improves health outcomes).²⁰ The 2000 report of the Secretary's Advisory Committee on Genetic Testing added an emphasis on social issues, leading to four components of evaluation represented by the acronym ACCE (for analytic validity; clinical validity;

clinical utility; and ethical, legal, and social implications; see Exhibit 1).²¹

The EGAPP Working Group, an independent, nonfederal group, integrated the ACCE framework and adapted more traditional processes and methods for evidence-based practice in medicine and public health developed by the USPSTF.²² A main objective of EGAPP is to synthesize and grade research conducted in multiple fields (such as laboratory sciences, epidemiology, economics, ethics, health services research, and behavioral and social sciences) as well as to identify knowledge gaps. Nevertheless, very little of this type of research or its synthesis has been published in the peer-reviewed literature. Indeed, between 2001 and 2006, we found that fewer than 3 percent of more than half a million published human genomics research studies fell in T2 research and beyond, presumably reflecting the amount of research being conducted, which in turn may indirectly indicate current research funding priorities.²³

Thresholds Of Evidence: Where Do We Draw The Line Between Research And Practice?

Important questions have been raised about defining the threshold for evidence that is sufficient to move a highly promising genomic application into routine clinical practice and how to get such an application reimbursed by third-party payers. It is likely that different applications will have different thresholds (for example, thresholds may be lower for rare conditions versus common diseases or for diagnostic versus predictive tests). In general, evidence-based medicine (EBM) has become the accepted standard for such decisions. Practitioners of EBM have developed standards, including a requirement for detailed evidence reviews before making recommendations. However, the world of genomics has been slow to embrace EBM. There may be several reasons for this. First, the field of medical genetics has, by and large, focused on rare genetic diseases for which there are an inade-

EXHIBIT 1 Domains In The Evaluation Of Genomic Applications Proposed For Clinical Practice

Domain	Element
Evaluation focus	Definition of the disorder/test/clinical scenario or intended use (for example, population tested, diagnostic or predictive)
Analytic validity (A)	Analytic sensitivity, specificity, predictive values, reliability and robustness
Clinical validity (C)	Gene-disease associations; clinical sensitivity, specificity, predictive values
Clinical utility (C)	Efficacy, effectiveness, safety, acceptability, efficiency, feasibility of implementation, costs
Ethical, legal, and social issues (E)	Confidentiality, privacy; access, stigmatization, discrimination

SOURCE: Adapted from J.E. Haddow and G.E. Palomaki, "A Model Process for the Evaluating Data on Emerging Genetic Tests," in *Human Genome Epidemiology: Scope and Strategies*, ed. M.J. Khoury, J. Little, and W. Burke (New York: Oxford University Press, 2004), 217–233.

quate number of individuals and families to study using randomized clinical trials or even well-conducted observational studies. Second, genetics has traditionally focused on a nondirective way of communicating information to diagnose and manage rare conditions for which there might not be effective interventions. Third, the recent rapid advances in genomics make the evaluation of tests a moving target that challenges traditional systematic-review methodologies.²⁴ Finally, the concept of “clinical utility” in genetics has been variably defined and measured.²⁵ Clinical utility, reflecting the balance between benefits and harms, can have multiple dimensions and interpretations in the context of genomics, from the traditional focus on improved health outcomes for an individual to other potential benefits for family members (such as counseling relatives about genetic testing). This latter consideration may loom large in the realm of genomics, where the value of information alone is often seen as adequate justification for testing.

■ **Low evidence threshold.** Let us consider two thresholds, as shown in Exhibit 2. The first is a low threshold for a genomic application to enter clinical practice even before T2 research has begun. It approximates the current state of affairs in the United States for many LDTs, as shown by the diabetes story described above. Based on current regulatory approaches, data on all components of evaluation are not required, and in many cases not available, for decision making by consumers, providers, and policymakers. Government regulation is limited, and, until recently, there has been no independent body, such as the EGAPP Working Group, to review evidence and make recommendations for test use. Thus, applications of genomic technologies can slip into the health marketplace with unknown benefits and potential harms and costs to individuals and society. For example, several genetic tests relating to nutrition, bone health, and cardiac health are sold directly to the general pub-

EXHIBIT 2
Characteristics Associated With Low And High Evidence Thresholds For Genomic Applications In Practice

Characteristic	Low threshold	High threshold
Analytic validity	Laboratory certification Validation data required	Regulatory oversight Systematic review of data
Clinical validity	No or limited data required	Systematic review
Clinical utility	No data required	Systematic review
Clinical guidelines	Expert opinion/professional guidelines	Evidence-based recommendation by independent group
Coverage and reimbursement	Highly variable	More consistent

SOURCE: A thorough review of processes of the current oversight system for genetic testing in the United States is provided by the Secretary's Advisory Committee on Genetics Health and Society, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services*, April 2008, http://www4.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf (accessed 6 June 2008).

NOTE: For explanation of low versus high thresholds, see text.

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lic. In national consumer and provider surveys conducted in 2006, the CDC found that 6 percent of the general population is aware of these tests, although less than 1 percent reported actually using them.²⁶ In 2006, a U.S. Government Accountability Office (GAO) investigation of such practices found major errors, discrepancies, and misleading information provided to consumers from several online genomic test offerings marketed directly to the general population.²⁷ Furthermore, once a genomic test is available, it may be used for purposes other than its intended use. In this case, there are no incentives for collecting crucial information on the test's performance and its health impact in the “real world” in terms of benefits and harms to individuals and populations.

■ **High evidence threshold.** On the other hand, if the threshold includes addressing all forty-four of the questions in the ACCE analytic framework using an evidence-based process, with an independent body evaluating all genomic applications, and comprehensive government regulatory oversight, fewer tests will be developed and become available in practice.²⁸ More-stringent requirements could delay access to potentially life-saving or otherwise clinically useful applications of new genomic tests. Although the rapid progress in the “-omics” fields makes the nature of the evidence a moving target, evidence pronouncements by professional groups, technology assessment groups, or government-sponsored groups can be important for access to and reimbursements of these tests and technologies by third-party payers.²⁹ A high evidence threshold could become a major disincentive for industry and academe to develop genomic technology.

■ **Finding a balance.** Fast and broad access needs to be balanced against safety, efficiency, and appropriate incentives for future innovation. The relatively large gray area that represents T2 research is already a challenge, particularly for defining the extent of validity and utility of genomic applications required for clinical practice, as well as for coverage and reimbursement.

As discussed earlier, it took more than ten years after the BRCA1 gene was discovered for the USPSTF to find sufficient evidence to allow it to make a favorable recommendation about its utility in practice for women with certain types of family histories. Before then, there was limited but sufficient fair-quality research published to determine the clinical validity of one clinical intervention: surgery to remove the breasts or ovaries, or both. However, there was insufficient research to determine the utility of other interventions, including increased screening or chemoprevention. By the time these recommendations were made, BRCA testing was established in clinical practice. The extent of use is uncertain, given that information systems do not exist in most populations to monitor the use of genetic tests.

What Is The Right Formula For Genomic Medicine?

Our current translation landscape in genomic medicine has major gaps. The science of gene discovery is relatively well funded and moving forward at a rapid pace, yet the translation sciences, including both clinical trials and large, well-designed observational studies, are lagging behind. Often, a gene discovery per se is simply assumed (incorrectly) to have clinical validity and utility for the practice of medicine (for example, genetic variants for susceptibility to diabetes, as discussed above).

■ **Investment in translation research.** Several steps can be taken immediately. The first is obviously more investment in translation research (especially in T2 and beyond), which historically has received much less support than discovery research in both genomics and other areas.³⁰ Since lack of evidence is the primary impediment to the translation of genomics into practice, research to provide that evidence is of paramount importance and represents the first step in addressing the evidence dilemma. This issue is well recognized and has been increasingly called for by many groups, including an Institute of Medicine (IOM) panel in the context of cancer biomarkers and HHS advisory committees, as discussed above.³¹ Increased translation research is also a component of the NIH Roadmap and FDA Critical Path initiatives.³² Translation research for genomics as for other technologies (especially T2 through T4) should be sponsored by government, by industry, and through private-public partnerships.³³ It can be done in health care settings or in community settings.³⁴ Both the NIH and the CDC will be funding projects related to translation of genome discoveries in 2008 and 2009.

■ **Continuous evaluation and synthesis.** Second, there needs to be increased emphasis on continuous evaluation and synthesis of the evidence that addresses the ACCE criteria, based on systematic reviews and meta-analyses conducted by evaluative processes such as the EGAPP initiative. Government agencies spend considerable resources in sponsoring discovery research, yet much less is spent on translation research and even less on evidence-based review, a legitimate and vital form of research, without which there can be no translation. Evidence reviews are crucial in telling us “what we know and what we do not know” at any given point about the validity and utility of genomic applications in practice. This information will be crucial to researchers, providers, patients, policymakers, and test developers and should be widely disseminated by scientific journals, professional organizations, government Web sites, and consumer and community organizations.

■ **A collaborative process for setting the evidence bar.** Third, we urgently need a collaborative process involving multiple stakeholders that sets the evidence bar for when genomic medical applications are ready for routine practice and identifies when selected genomic applications might be conditionally introduced into practice until translational research definitively establishes their value. The appropriate evidentiary threshold for practice needs to be vigorously addressed and cali-

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brated, since neither the low nor the high thresholds we have presented are optimal. The main issues to solve are (1) which of the forty-four questions in the ACCE analytic framework for evaluating the use of a genomic test can be left out of consideration; (2) what type of evidence is needed; (3) what type of review process conducted by what type of group is adequate; and (4) what levels of government oversight and regulation are required. The answers will vary depending on the characteristics of the genetic applications under consideration and what is already known about the tests. Ultimately, we need to raise the threshold from the low bar that now exists and decide how to maximize the opportunity for health benefits from genomic medicine while minimizing harms. Obviously, this would require deliberation to get input from all stakeholders (including consumers). Although there are no clear evidentiary thresholds in genomics for safety, efficacy, or value, government and the private sector must jointly develop decision rules based on clear-cut criteria that could be different for various tests and their intended uses. In the meantime, the SACGHS and other groups have recommended more FDA oversight of LDTs, to avoid the introduction of poorly validated tests.³⁵

■ **Development of “conditional” insurance coverage.** The process should also consider the development of an evidence threshold for a translation research model. Many genetic tests will be in T2 research for years to come. A new model for the integration of selected genomic applications into practice as translation research could speed the translation of promising tests. An important ingredient of this model is the development of a process for “conditional” insurance coverage based on new evidentiary thresholds. Over the past few years, several groups have developed new models for the implementation of translation research through risk sharing. The term “coverage with evidence development” (CED) has been used by the Centers for Medicare and Medicaid Services (CMS) under certain scenarios and has been recommended by the IOM for the development of cancer biomarkers.³⁶ This implies that additional data should be collected under research protocols as part of observational and clinical trials, while these tests are covered temporarily by third-party payers “in certain circumstances to facilitate controlled and limited use of... tests until sufficient evidence can be gathered to make an informed decision about standard (permanent, non-provisional) coverage.”³⁷ The implementation of CED has been difficult, necessitating additional guidance from the CMS on the types of CED and how coverage may be determined. In practice, the current concept of CED as used by the CMS applies only to a limited number of high-impact and high-cost technologies; therefore, an expansion would be required to cover promising genomic applications.

■ **A look abroad.** Finally, we may also wish to look at the experiences of other

countries as they grapple with similar issues. Standards for what constitutes high-quality evidence are increasingly derived from international consensus, although implementation varies widely in response to different countries' national health care structures, priorities, and public attitudes about new technologies. The United States can undoubtedly learn from how other countries address both the evidence threshold and diffusion into clinical practice.

■ **A solution soon.** For the long-term viability of genomic medicine, a solution to the thorny evidence threshold problem needs to emerge soon. Independent groups such as the EGAPP Working Group are already making progress in exploring the feasibility of delineating evidence thresholds for different applications. If implemented properly, newer collaborative approaches among stakeholders can begin to address the current dilemma in genomic medicine. The recent HHS initiative on personalized health care that integrates genomics with health information technology (including electronic health records) will accelerate the future conduct of such translational research and surveillance in health care settings.³⁸

NOW IS THE TIME TO ESTABLISH A FLEXIBLE and sustainable process for translation research and evaluation of promising genomic applications, with concomitant development of a workable mechanism for guiding coverage decisions. A major expansion of the U.S. clinical translation research and evaluation enterprise has been needed since long before the Human Genome Project began.³⁹ This enterprise has become an absolute necessity in the genomics era, to accelerate the appropriate integration of genomics into the practice of medicine and public health in the twenty-first century.

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 37. Jones and Wells, "Strategies for Academic and Clinician Engagement."
 38. DHHS, *Personalized Health Care: Opportunities, Pathways, Resources*, 2007, <http://www.hhs.gov/myhealthcare> (accessed 18 August 2008).
 39. N.S. Sung et al., "Central Challenges Facing the National Clinical Research Enterprise," *Journal of the American Medical Association* 289, no. 10 (2003): 1278–1287.