Genome-Based Diagnostics: Clarifying Pathways to Clinical Use: Workshop Summary

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Steve Olson and Adam C. Berger, Rapporteurs; Roundtable on Translating Genomic-Based Research for Health; Board on Health Sciences Policy; Institute of Medicine

GENOME-BASED DIAGNOSTICS

Clarifying Pathways to Clinical Use

WORKSHOP SUMMARY

Steve Olson and Adam C. Berger, *Rapporteurs*

Roundtable on Translating Genomic-Based Research for Health

Board on Health Sciences Policy

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Willing is not enough; we must do."
—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the process. We wish to thank the following individuals for their review of this report:

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Although the reviewers listed above have provided many constructive comments and suggestions, they did not see the final draft of the report before its release. The review of this report was overseen by **Harold J. Fallon,** Dean Emeritus of the University of Alabama at Birmingham School of Medicine. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author and the institution.

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The Roundtable wishes to express its gratitude to the expert speakers whose presentations helped outline the challenges and opportunities in developing clinically useful genomic diagnostic tests. The Roundtable also wishes to thank the members of the planning committee for their work in developing an excellent workshop agenda. The project director would like to thank project staff who worked diligently to develop both the workshop and the resulting summary.

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Abbreviations and Acronyms

AHRQ	Agency for Healthcare Research and Quality
BRCA1	breast cancer type 1
BRCA2	breast cancer type 2
CAP	College of American Pathologists
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CED	coverage with evidence development
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare & Medicaid Services
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
FDA	U.S. Food and Drug Administration
GAPPNet	Genomic Applications Practice and Prevention Network
GP	general partner
IDE	investigational device exemption
IND	Investigational New Drug
IOM	Institute of Medicine
IRB	institutional review board

LDT	laboratory-developed test
LP	limited partner
NCCS	National Coalition for Cancer Survivorship
NIH	National Institutes of Health
NVCA	National Venture Capital Association
ODAC	Oncologic Drugs Advisory Committee
PMA	premarket approval
PSA	prostate-specific antigen
RCT	randomized controlled trial
SACGHS	Secretary's Advisory Committee on Genetics, Health, and Society
USPSTF	U.S. Preventive Services Task Force

1

Introduction[1]

The sequencing of the human genome and the identification of associations between specific genetic variants and diseases have led to an explosion of genomic-based diagnostic tests. These tests have the potential to direct therapeutic interventions, predict risk or onset of disease, or detect residual disease. As research progresses and an increasing number of associations are found, further tests will be developed that can aid in providing personalized treatment options for patients.

However, the adoption of genomic diagnostic tests by health care providers has been limited due to a lack of evidence regarding the clinical utility of many tests.[2] Health funders and practitioners lack the data necessary to distinguish which tests can improve practice or the clinical settings in which tests will provide the greatest value. The Roundtable on Translating Genomic-Based Research for Health held a workshop in November 2010 (IOM, 2011b) to determine what evidence is needed and how it is viewed by different stakeholders in order to develop genomic diagnostic tests of clinical value.

Many workshop participants noted that evidence is lacking for the

[1] The planning committee's role was limited to planning the workshop, and the workshop summary has been prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants, and are not necessarily endorsed or verified by the Institute of Medicine, and they should not be construed as reflecting any group consensus.

[2] Formally, a diagnostic test confirms a specific condition, while a prognostic test predicts the possibility of developing a specific condition. This report uses "genomic diagnostic test" to refer to any genetic or genomic test used in making health care decisions.

impact of most genetic and genomic tests on health outcomes and that better mechanisms are needed to generate this evidence. "If you look at many of the evidence-based reviews in the literature, insufficient evidence is one of the predominating assessments of most of the tests currently on the market," said Debra Leonard of Weill Cornell Medical Center in recounting that meeting.

Different stakeholders presented new models, strategies, and specific actions for generating evidence for genomic diagnostic test development. For example, workshop participants looked at whether combining evidence from different studies would generate sufficient evidence to meet stakeholder requirements for analytic validity, clinical validity, and clinical utility (these terms are defined in Chapter 2 of this report) as compared to the evidence generated from a single good clinical trial. The evidence should only need to be "adequate," said Leonard, "not perfect." The evidence should be strong enough to "get us to 85 percent, 'B grade,' certainty for these tests."

New economic models for reimbursement were discussed in which a test's value would be determined by its ability to direct clinical care, such as preventing the use of ineffective therapies or directing patients to therapies that improve outcomes, as opposed to the cost of performing the test. Participants discussed implementing a system that does not pay for a treatment if the treatment is not supported by prognostic or predictive tests. "This is a huge issue in the United States," observed Leonard. Health care costs now constitute 17 percent of the U.S. gross domestic product, yet the U.S. health care system is ranked the lowest in outcomes and the most costly among developed countries (Peterson and Burton, 2007; SSAB, 2009). An ongoing global economic crisis demands fiscal responsibility, said Leonard, which is driving efforts to improve the cost-effectiveness of the health care system. "There's a very negative approach to rationalization of health care in the United States. We need to think about how to address that."

The previous workshop also sought to address the variance in stakeholder evidentiary requirements, specifically probing whether demonstration of safety and efficacy is enough to justify use of a new genomic test in medical practice or whether tests need to demonstrate clinical utility or cost-effectiveness instead. The Roundtable on Translating Genomic-Based Research for Health held a follow-up workshop on November 15, 2011 titled *Facilitating Development and Utilization of Genome-Based Diagnostic Technologies* to further explore the differences in evidence required for clinical use, regulatory oversight, guideline inclusion, coverage, and reimbursement of genomic diagnostic tests among stakeholders with the goal of clarifying a pathway for successfully bringing tests to clinical use for

the benefit of patients.[3] Presenters at the workshop were asked to consider four broad issues:

1. How are the barriers to successful genomic test development viewed?
2. What are potential solutions?
3. What are the obstacles to achieving those solutions?
4. How can those obstacles be overcome?

This report summarizes the presentations and discussions that took place throughout the workshop. Chapter 2 relates two presentations which sparked extensive discussion. One presentation proposed that all genomic diagnostic tests be reviewed and approved by the U.S. Food and Drug Administration (FDA; see Box 1-1). The other observed that venture capitalists are no longer investing substantially in the development of genomic diagnostic tests because of a lack of clarity surrounding regulatory and reimbursement pathways. Though the two talks may seem only distantly related, both suggested the need for major changes in the systems used to develop, regulate, and reimburse genomic diagnostic tests.

The next four chapters present the perspectives of different stakeholders in the development of genomic diagnostic tests. Chapter 3 addresses the concerns of test developers; Chapter 4 those of patients; Chapter 5 those of payers; and Chapter 6 those of government officials. Each stakeholder group has a different set of needs and issues of importance, yet commonalities among them are apparent, such as the need to put patients and health outcomes at the center of discussion and action.

Chapter 7 summarizes the rich and extensive discussions that occurred throughout the workshop. These discussions have been organized thematically, with the identification of speakers who made specific proposals and recommendations. Collectively, the participants at the workshop charted a variety of ways to move forward in developing genomic diagnostic tests that could substantially improve human health.

[3] The full statement of task can be found in Appendix C.

BOX 1-1
Pathways to Approval and Use

Decisions by FDA to clear or approve medical devices, including genomic diagnostic tests, for marketing are based on the safety and effectiveness of the product. The Medical Device Amendments of 1976 implemented a three-tier system. Class I devices are common, low-risk devices that are generally exempt from premarket evaluation by the agency. Class II devices are moderate-risk devices that are subject to premarket notification (also known as the 510(k) process), in which the sponsor must demonstrate substantial equivalence of the device to an already marketed product. Class III devices are the most complex and present the highest risk; makers of Class III devices must submit a premarket approval application demonstrating safety and effectiveness and obtain FDA approval prior to marketing.

Initially, genetic tests focused on single genes. The in vitro diagnostics industry was not very interested in developing such tests because they typically constituted a small market with poor reimbursement, according to Leonard. As a result, genetic tests were developed largely by clinical laboratories using standard molecular biology methods. These laboratory-developed tests (LDTs) tended to be based on published genotype-phenotype correlations, were developed using a set of patient and control samples, and usually were produced in small volumes. They were performed by specialists with advanced training and usually required expert interpretation. LDTs generally were and still are developed under the provisions of the Clinical Laboratory Improvement Amendments (CLIA) without clearance or approval from FDA.

Today's genomic tests are quite different. They often are based on complex testing algorithms that encompass multiple genetic variants, genes, or gene expression patterns and, most recently, whole-exome or whole-genome sequencing, said Leonard. The results are used not only for diagnosis but for the selection of therapies, dosing decisions, prognosis, and detection of residual disease. Tests are increasingly empirical and nontransparent and rely on complex statistical methods. They often require complex software, many incorporate automated interpretation, and their clinical validity is not well understood (Wright and Kroese, 2009). Novel tests are often developed by companies and "licensed" to a laboratory, the volume and types of LDTs have grown significantly, and they are often a mechanism for the market entry of novel tests. A higher proportion come from commercial laboratories and biotechnology companies, and they often do not involve a close relationship between clinicians, pathologists, and patients. Some tests are broadly advertised and aggressively marketed to clinicians. Others are marketed directly to consumers and are available over the Internet with overnight shipping (Meyers, 2011). They can have a national or even international reach.

2

Calls for Change

Important Points Highlighted by the Individual Speakers

- The undervaluation of tumor biomarkers reduces the use of diagnostic tests as well as incentives to develop evidence about their effectiveness.
- Eliminating the LDT pathway and submitting all genomic tests to a rigorous regulatory process could result in the generation of high-quality evidence regarding the analytical validity and clinical utility of all such tests.
- Venture capital companies are no longer investing in the development of molecular diagnostic tests because of the complexity in and lack of clarity for both regulatory and reimbursement pathways.
- A predictable and efficient pathway, not necessarily an easier one, from regulatory approval to reimbursement could help attract further venture capital investment in this space.
- Standards for molecular diagnostics could help establish widely accepted regulatory and reimbursement pathways that test developers can follow.

While reflecting their own viewpoints, two speakers framed much of the day's discussion. Daniel Hayes, from the University of Michigan Comprehensive Cancer Center, challenged the workshop participants to consider

a system in which all genomic diagnostic tests are approved through FDA rather than going through the LDT pathway. Sue Siegel, with the venture capital firm Mohr Davidow, said that venture capital funds are currently reluctant to invest in life sciences and health care start-ups, including molecular diagnostics, because of the continued lack of clarity surrounding the regulatory and reimbursement areas. Both speakers called for major changes in the regulation of genomic diagnostic tests to ensure that the field continues to move forward.

A CONSOLIDATED SYSTEM OF REVIEW AND APPROVAL FOR GENOMIC DIAGNOSTIC TESTS

Oncologists overtreat probably 75 percent of their patients, according to Hayes, because they often do not know which patients are going to benefit from which therapies. "We treat everybody in the hopes that we'll hit the ones that need it and will benefit. I tell my post-docs that luck is not a good strategy in golf or science. It's nice to have when you get it, but it'd be really nice if we could focus our treatment on patients and not just hope that we get lucky."

A bad diagnostic test for a tumor biomarker is as harmful as a bad drug, Hayes pointed out. He asked whether physicians would use a drug if they were not sure how it was mixed or what its concentration was, if they did not have clinical data about how the drug might be used, and if they did not have reliable clinical research data to determine how much efficacy it might have. "Of course not, but every day of the week we see patients whose treatment is being altered by tumor biomarkers in the absence of really good data to support that."

The basic problem is that there has been relatively little consistency regarding which biomarkers have been introduced into clinical practice. Very few cancer biomarkers with demonstrated clinical utility have been introduced over the past 30 years. Even among those tests that have been integrated into practice, their use in certain settings has not always been supported by evidence of benefit, such as the use of prostate-specific antigen (PSA) as a screening test (Andriole et al., 2009), said Hayes. This has helped to create what Hayes has termed a "vicious cycle" in which tumor biomarkers are systematically undervalued (Figure 2-1). This undervaluation has led to limited use of these diagnostics by health care providers and poor reimbursement when a marker has been able to navigate the regulatory environment to be brought to market. Lack of use and reimbursement in turn leads to limited funding for biomarker research because the return on investment is low. The perception that markers have little utility has also led to an environment of lower academic recognition for developing biomarker-based tests. The overall result is reduced ability and incen-

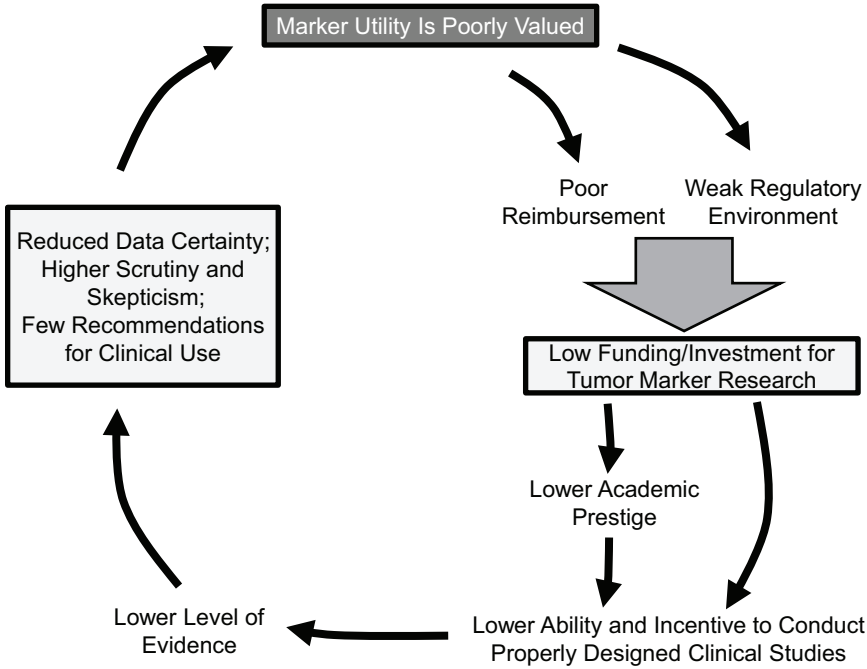

FIGURE 2-1 Undervaluation of tumor markers leads to a vicious cycle in which incentives do not exist to increase the valuation.
SOURCE: Hayes, IOM workshop presentation on November 15, 2011.

tive to conduct properly designed clinical trials to generate high-quality evidence of clinical utility. In return, there is reduced data certainty, higher skepticism, and few recommendations for clinical use, said Hayes, which completes the cycle by contributing to the poor valuation of marker utility.

Hayes focused his recommendations for breaking the "vicious cycle" of undervalued tumor biomarkers on two areas: the regulatory environment and marker reimbursement.

Requiring FDA Approval of Laboratory Developed Tests

LDTs can currently be introduced into clinical practice while only meeting Clinical Laboratory Improvement Amendments (CLIA) laboratory standards (see Box 1-1). Such tests do not undergo formal reviews of analytical validity, clinical validity, or clinical utility (Box 2-1 and Table 2-1). Hayes recommended elimination of this pathway for market entrance and, instead, would require all diagnostic tests to undergo FDA review and

BOX 2-1
Definitions of Validity and Utility

During his presentation, Hayes offered definitions of analytical validity, clinical validity, and clinical utility adapted from Teutsch et al. (2009)

- **Analytical validity:** The assay accurately and reproducibly measures what it intends to.
- **Clinical validity:** The assay identifies a biological difference that may or may not be clinically useful.
- **Clinical utility:** Results of the assay lead to a clinical decision that has been shown with a high level of evidence to improve outcomes.

approval. Many commonly used tests would be removed if this were to occur, noted Hayes, especially in situ tissue-based tests, but it is not clear how many of these tests have analytical validity, clinical validity, or clinical utility, he said. While Hayes acknowledged that elimination of the CLIA pathway may be met with opposition from various groups and individuals, he also observed that "I can't come up with a new drug in my [laboratory] as long as I only give it to my patients. That's against the law, and I think it should be against the law to develop a new assay and use it to treat my patients differently without having had it vetted by some regulatory body."

TABLE 2-1 Comparison of CLIA and FDA Regulatory Pathways

	CLIA	FDA
Research Phase	No	Yes
Analytical Validation	Post hoc sampling	Yes
Clinical Validation	No	Yes
Report Adverse Events	No requirement; no system	Yes
Transparent Results	No public information	Published review summary

NOTE: CLIA, Clinical Laboratory Improvement Amendments; FDA, U.S. Food and Drug Administration.
SOURCE: Gutierrez, IOM workshop presentation on November 15, 2011.

A New Basis for FDA Approval

FDA approval of diagnostic tests is currently based on evaluation of intended use, analytical validity, and clinical validity. In advocating that FDA review and approve all diagnostics before they can be introduced into clinical practice, Hayes also recommended that a higher evidentiary threshold be met for diagnostic tests. Instead of including clinical validity and intended use in their assessment, he suggested that FDA should review diagnostics for analytic validity and clinical utility. While he acknowledged this will increase the time and resources needed to get FDA approval, tests will have demonstrated clinical value for patients upon entrance to clinical practice.

This change would require following one of three pathways for generating high-quality evidence of clinical utility, Hayes said (Figure 2-2). One is through a prospective-retrospective study using archived specimens from a clinical trial that can be used to specifically address the question being studied (IOM, 2011b; Simon et al., 2009). If archived specimens do

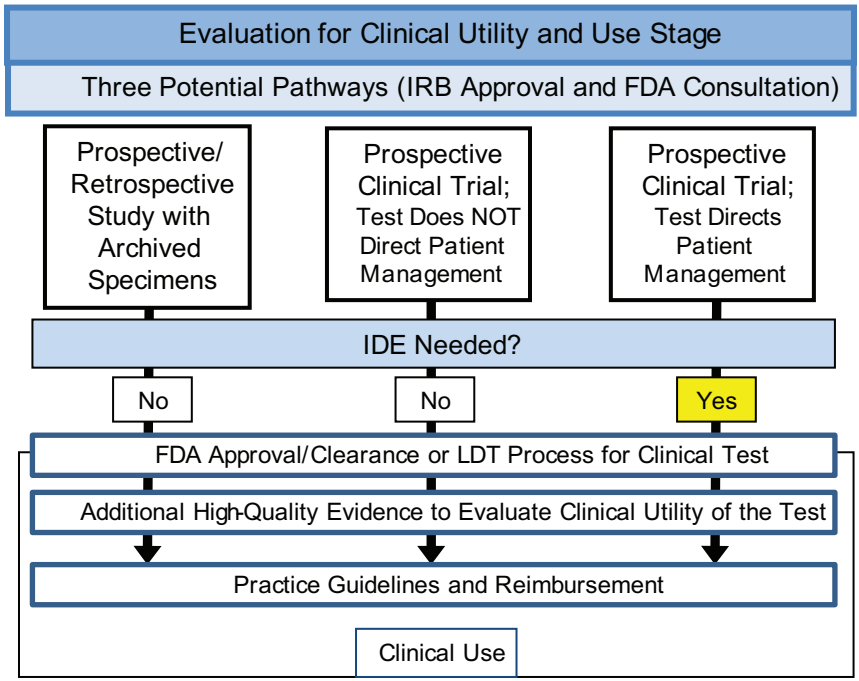

FIGURE 2-2 Three pathways for generating high-quality evidence of clinical utility. SOURCE: As adapted from IOM, 2012.

not exist, evidence could be generated either through a prospective clinical trial where the marker does not direct patient management or through a prospective clinical trial where the marker does direct patient management. These three approaches would each generate high-quality evidence for the intended clinical use of a tumor biomarker test upon which FDA could base its review and approval or disapproval. This same evidence could then be used by technology assessment groups, practice guideline developers, and payers for decision-making purposes.

Hayes admitted that determining clinical utility is still somewhat like art: "I don't know what it is, but I know it when I see it." The results of the assay will need to lead to a clinical decision that has been shown with a high degree of evidence to improve outcomes. "For each circumstance, for each disease and for each assay, one needs to decide if it reaches what a group of clinicians would call clinical utility."

Consolidate Reviews Within FDA

Currently, drugs are evaluated for safety and effectiveness in the FDA Center for Drug Evaluation and Research (CDER) while devices that are not linked to specific therapeutics are evaluated in the FDA Center for Devices and Radiological Health (CDRH). While CDER has established a standing Oncologic Drugs Advisory Committee (ODAC) made up of experts in oncology and statistics, patient advocates, and other representatives to help review marketed and investigational cancer drug products, a similar approach has not been adopted by CDRH, according to Hayes. The center has enormous analytical expertise but weaker oncologic expertise. Instead of a standing board, ad hoc committees of experts without a "corporate memory" review devices, which means that "there is no consistent approach toward how one device is approved versus the other." Hayes did note that while the ODAC has significant oncologic expertise it lacks analytical expertise and proposed combining the review of all oncologic products into a single FDA Oncology Office. Combining all oncologic products into a single office would require a fundamental reorganization of FDA, Hayes observed, which is a substantial obstacle to moving forward on this recommendation.

Basis for Reimbursement

Hayes recommended that reimbursement be based on the value that a tumor biomarker provides for clinical decision making as opposed to the cost of performing the assay. Cost-effectiveness analyses and comparative effectiveness research would be needed to demonstrate that the benefit to patients, society, and payers far outweighs the cost of a tumor biomarker

with demonstrated clinical utility. Third-party payers would need to provide reimbursements that recoup the increased costs associated with generating high-quality evidence of clinical utility. However, Hayes noted that health care providers also need to reform their practices and ensure they are properly using and ordering tests. "Third-party payers should have to pay for a test that has clinical utility, but shouldn't have to pay for a test that is used in the wrong way."

Overcoming Barriers

Overcoming the barriers to these recommendations will involve many stakeholders, including regulatory agencies, third-party payers, pharmaceutical companies and other commercial entities, physicians and other caregivers, patients and patient advocates, clinical guideline and technology assessment panels, academic centers and investigators, and research funding entities. These groups need to be "in the room talking to each other and working out the problems," said Hayes. Together they could break the vicious cycle of undervaluation and create a virtuous cycle by introducing tumor biomarkers with high clinical utility (Figure 2-3), Hayes concluded.

PERSPECTIVE FROM VENTURE CAPITAL

Because of the complexity and uncertainty that currently surrounds regulation and reimbursement, the venture capital community is reluctant to invest in the development of molecular diagnostics, said Siegel. "We will continue to invest in the companies and their products that we currently are invested in, but the money is fleeing. Venture takes the early risk. Who is going to fill in when . . . venture capital is fleeing?"

Many earlier tests were developed with support from venture capital, including the Oncotype DX breast cancer assay for predicting chemotherapeutic benefit and metastasis risk, the MammaPrint assay for the risk of metastasis following breast cancer surgery, and the HER-2/neu test for directing Herceptin treatment of women with metastatic breast cancer.

More broadly, Siegel observed, the venture capital community plays a crucial role in the economy, spurring innovation that benefits the quality and efficiency of the health care system. From 1970 to 2010, the amount of revenue generated by venture-backed companies was 21 percent of the U.S. gross domestic product. Approximately 12 million jobs in venture-backed companies led to $3.1 trillion in revenue. About three-quarters of biotechnology jobs are within companies that were originally venture-backed, and 80 percent of the revenue in biotechnology is generated from these companies.

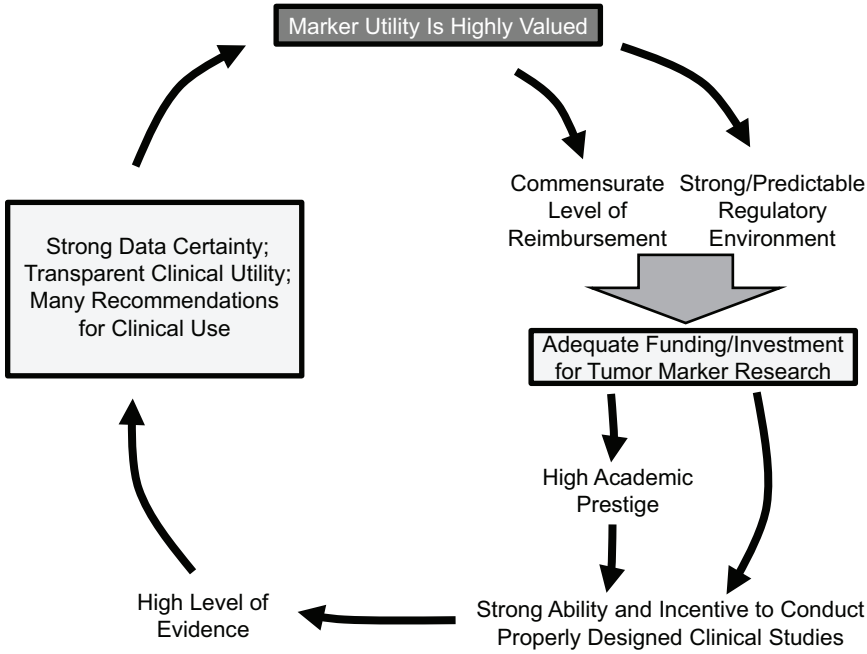

FIGURE 2-3 Highly valued tumor biomarkers lead to a virtuous cycle in which markers are continually improved.
SOURCE: Hayes, IOM workshop presentation on November 15, 2011.

The Venture Capital Process

Siegel gave a brief overview of the venture capital process. It begins with limited partners (LPs), who manage pools of money such as pension funds, retirement funds, endowments, or private wealth. LPs deploy these funds into different asset classes, of which venture capital is one. Venture capital tends to take the highest risk but in doing so also tends to get the highest rewards.

LPs fund general partners (GPs) who are investing in particular areas. The GPs deploy that money into entrepreneurs and companies, which provide products and services (Figure 2-4). As these companies grow, they generate assets that can be returned to the LPs. In this way, the LPs recoup their investments.

Siegel used her own firm as a more specific example. Mohr Davidow is a Silicon Valley venture firm that has existed for about three decades. It invests in three areas: information technology, clean technology, and personalized medicine. The firm bases its investment decisions on markets,

people, and technology, among other criteria, said Siegel. It tends to favor big problems that need solutions in big markets. As an early stage investor, the firm expects a life science or health care company to have a capital-efficient business model, to produce a product, and to be generating revenue within 3 to 5 years. It also prefers the company to have a strong intellectual property position, limited regulatory risks, a clear path toward reimbursement, and a convincing health economics model (a strong rationale for why a product could help the whole system of health care decrease costs).

With molecular diagnostics that are developed and brought to market under CLIA, venture capitalists can understand the risks and timelines required to grow a company and develop the tests as well as be able to predict with some confidence the potential returns, according to Siegel. Creating a company from inception with the purpose of developing and fully commercializing an LDT can take up to $100 million plus to get to a breakeven point, though some companies have managed to do it for $60 million to $70 million, "but they are more the exception than they are the rule." To found a company with the purpose of developing an FDA-approved test would require somewhere between $100 million and $150 million of total capital invested to get the company to a breakeven point. Venture capitalists consider a return of only three times their investment into a company to be an unexceptional return. Therefore, a start-up company requiring $100M of total capital invested from its inception to develop and fully

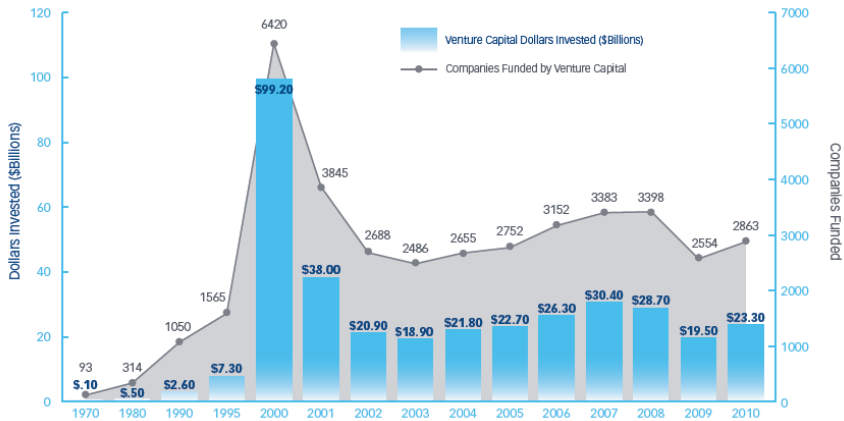

FIGURE 2-4 Venture capital investments in U.S. companies from 1970 to 2010. SOURCE: NVCA, 2011a.

commercialize a test needs to return at least $300 million within a fairly short timeframe to even meet what would be considered a modest return.

The Need for Clarity

The venture capital community is not asking for less stringent regulations. "We're not here, as venture capitalists, to tell you don't make it hard. We all want safe products," Siegel said. "We're here to ask you to make it clear, because without clarity we can't assess the risk of knowing when to invest or when not to invest."

Regulatory and reimbursement uncertainty has contributed to a precipitous decline in venture capital investments in the life sciences and health care (Figure 2-5) and current trends point to future declines. In a survey of 156 venture capitalists about investing in the life sciences, 40 percent reported decreasing their life science investments over the past 3 years with an additional 40 percent planning to decrease their investments over the next 3 years (NVCA, 2011b). Sixty percent indicated that regulatory challenges are having the most impact on their investment decisions. Forty percent said that they planned to invest more in Asia and Europe. "Even though some regulations might be tougher [there], they're clearer and [companies] know how to get reimbursed," Siegel said. "Here in the [United] States, it's not clear that we can get reimbursed for molecular diagnostic tests. So better predictability and increased efficiency [is needed]."

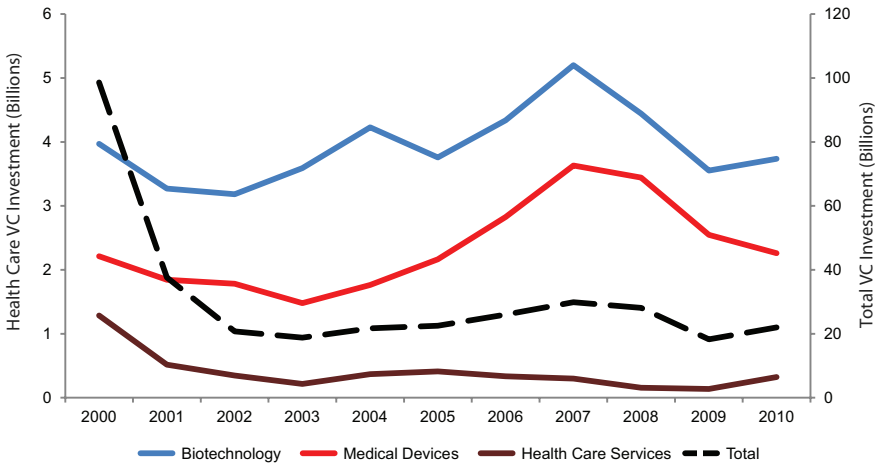

FIGURE 2-5 Venture capital investments in the life sciences and health care have declined significantly in recent years.
SOURCE: As adapted from NVCA, 2011c.

Reimbursement is currently a tougher obstacle than regulation, said Siegel. Companies cannot be sure whether their products will be reimbursed. Reimbursement has become "a truly Sisyphean effort," and getting coverage decisions whether regional or national can be difficult, said Siegel. When drugs get through Phase III development, the Centers for Medicare & Medicaid Services (CMS) generally approves their reimbursement, but currently no such process exists for molecular diagnostics.

FDA and CMS also need to define the reimbursement pathway for molecular diagnostics. "What we're asking for is a predictable and efficient roadmap from FDA to CMS. This allows private payers to then have a baseline to benchmark against," said Siegel.

People in other industries such as the semiconductor industry have worked hard to develop standards to enable their products to move forward; the same needs to happen with molecular diagnostics. New approaches with companion diagnostics have been helpful, but much more progress is needed. In particular, said Siegel, the National Institute of Standards and Technology should be developing biological standards.

Siegel also pointed to the value of biological samples.[1] She urged that a national repository with guidelines be put in place to allow for the accessing of biological samples so that studies can be done in a more standardized way.

The Consequences of Inaction

Without greater clarity, funding for innovation will dry up, job growth will slow, the transition of the health care system toward prevention and lower costs will not take hold, and national competitiveness will be eroded. "People are going elsewhere in the world to launch products or set up companies. It's happening today. It's happening pretty aggressively." Even if patient advocate groups organize funding for the development of diagnostics, who will coach the entrepreneurs and help them develop their business plans and build their companies, asked Siegel.

Siegel urged that venture capitalists continue to be included at meetings on molecular diagnostics. "The more you educate us about what the decision process will be, the better the investment decisions we can make. This will allow venture capital firms to continue to support health care entrepreneurs who bring innovative ideas and business models that can help transform our current health care system into one that offers improved quality of care and increased access at lower costs."

[1] The Roundtable on Translating Genomic-Based Research for Health held a prior workshop on July 22, 2010, titled Establishing Precompetitive Collaborations to Stimulate Genomics-Driven Product Development, which examined the value, utility, and ethical challenges in using biospecimens in developing medical products, including diagnostics (IOM, 2011a).

3

Test Developers

Important Points Highlighted by the Individual Speakers

- Regulation of genomic diagnostic tests can be a critical factor in the extent of use of those tests and in the competitiveness of companies.
- Standards, quality control, regulatory guidelines, and technology assessments all can facilitate the movement of a test from bench to bedside.
- Any coverage and reimbursement reform should recognize the value of advanced medical diagnostic tests, their impact on health care, and the resources needed to develop and validate them.
- Establishing the value of a test requires that its use be compared to traditional practices.

Four speakers at the workshop addressed the development of genomic diagnostic tests from the perspective of test developers. All pointed to the need to develop better evidence regarding the value of a test, which in turn can affect coverage and reimbursement. They also called for clear regulatory standards to guide test development.

REGULATORY CLARITY IN A COMPETITIVE MARKETPLACE

Quest Diagnostics is one of the world's leading providers of diagnostic testing, information, and services. The company serves half of U.S. physicians and receives samples from half of U.S. hospitals every day. In addition to providing clinical services using both laboratory developed and FDA approved tests, Quest develops LDTs under CLIA requirements and commercializes in vitro diagnostic kits under FDA oversight. Quest also provides genetic counseling services for physicians, works closely with major pharmaceutical companies to facilitate the introduction of new therapeutics and companion diagnostics, provides electronic health records for health plans and patients, and even has a smart phone app that allows patients to receive their own test results. "We deliver high-impact, high-value, low-cost information to the health care system," said Nicholas Conti of Quest.

Conti and his colleagues are responsible for evaluating new technologies that will become clinical diagnostic tests to be offered by Quest. They are interested in any field of medicine and in all disease states, since "genomic-based testing impacts all of them."

Innovation and Competitiveness

Reducing costs and delivering services based on evidence of value are vital to health care in the 21st century, said Conti. Tremendous innovations are occurring not only in the technologies used to discover new biomarkers, but also in their application to clinical practice. In an increasingly global marketplace, delays or friction points involving regulation or reimbursement can compromise a company's competitive standing and ability to create sustained high-paying jobs.

Improving Rather Than Adding Regulation

Overwrought regulation or limits to physician discretion could stifle innovation and the practice of medicine. Increased regulatory oversight and the application of evidence-based protocols are worthwhile goals, said Conti, but the issues are complex and long-standing. The current system by which LDTs are regulated by CMS under CLIA has yielded many diagnostic innovations that have radically improved the practice of medicine. HIV testing, genetic tests for mutations causing hypertrophic cardiomyopathy, and screening tests for neurological conditions, for example, are all based on LDTs.

The practice of medicine would be dramatically changed if all tests were required to obtain FDA approval, according to Conti. For certain medical specialties, the generation and scope of evidence vary greatly, par-

ticularly where the adoption cycle is quick and the peer-reviewed literature is critical. The testing pipeline in these disciplines would dry up, he said, and many LDTs that are already incorporated into practice guidelines would disappear. For example, with infectious diseases, mutations occur at a rapid pace, which infectious disease specialists use to track and treat disease. In such cases, if companies were required to go through an FDA submission process, by the time approval is gained, the product would no longer be useful.

The incentives for diagnostic companies to develop some of these tests as FDA-approved kits are also lacking, with companies citing too small a market and prohibitive study costs for many of the tests. If a good study for a low-volume test can demonstrate concordance with the published literature, developing that test and bringing it to market is not as costly an endeavor, said Conti. There is a need to balance increased regulation with its affects on medical practice and innovation. "That is really where the value of CLIA comes in."

The important question to ask is not whether there should be more regulation, but rather is it better regulation? Can duplicative regulatory efforts be eliminated? Can the existing system be improved rather than constructing a new system? "That's the discussion we need to have," said Conti.

Protecting Physician Discretion

Limiting the incentive to develop or access innovative tests could hamper advances in patient management, according to Conti. The medical system in the United States is grounded on the concept that physicians are the arbiters of medical care. In the interests of their patients, they will exercise their medical discretion in ordering, interpreting, and delivering diagnostics, therapies, and other forms of care. Reference laboratories such as Quest provide physicians with access to tests for which published research indicates that the test can improve the care of patients. Potential interference with this discretion "should be considered with the greatest of caution."

Solutions to the Problems

Conti offered several solutions to the problems currently facing the development of genomic diagnostics. First, genomic test development needs clear regulatory certainty. Federal regulation should not be duplicative, as would be the case if FDA had to clear LDTs. Instead, legislation should build on what works by modernizing CLIA. Agency decision making should be transparent, with rulemaking by notice and comment rather than through

guidances. People who are qualified in both the public and private sectors should come together to discuss problems and develop solutions.

Finally, stakeholders should be patient and allow some of the initiatives currently under way to progress. Conti cited recent work by the American Medical Association to develop CPT codes for multivariate tests (AMA, 2011), CMS's modification to reimbursement procedures for CPT code stacking (CMS, 2012), and the development of the National Institutes of Health (NIH) Genetic Test Registry as examples (NIH, 2010).

IMPROVING THE EFFICIENCY OF TEST DEVELOPMENT

MammaPrint is a multigene index assay that uses the gene activity of a tumor sample to identify the risk of recurrence for an individual breast cancer patient, said Laura van 't Veer of the University of California, San Francisco. She drew upon her experience in developing the MammaPrint test to discuss increasing the efficiency of bringing a test from research discovery to clinical use.

The movement of a genomic test from bench to bedside has two important end points, van 't Veer said. One is the use of the test in clinical trials and the second is the commercialization of the test. The path from discovery to clinical trials involves discovery, confirmation of research, independent validation, quality assurance, regulatory oversight, and the initiation of a trial with a clinical trial group. To commercialize a test, additional steps are needed which include technology assessment, the development of guideline recommendations, a determination of cost-effectiveness, and agreement by the health care system to reimburse the use of the test.

Standardization of validation protocols will facilitate the efficient development of genomic-based tests, stated van 't Veer. She and her colleagues early on began working with clinical trial groups to conduct independent validation using external audits and a predefined statistical protocol in the development of MammaPrint (Buyse et al., 2006). The purpose of the initial validation was to demonstrate the robustness of the risk assessment and to establish a background for the subsequent clinical trial. Many of the data used in the independent validation were separately evaluated by experts in informatics, clinical data, pathology, and statistics. Particularly important are predefined acceptance criteria, which show that a test is being validated and reviewed by external parties. "A lot of the literature that is currently around on validation of genomic tests doesn't include all the independent steps, and independent review, as we've learned over the years, is very crucial."

A second opportunity for improved efficiency lies in quality control. Quality assessment for clinical trials involves a number of technical features, including precision, reproducibility, repeatability, accuracy, sensitiv-

ity, and robustness. Software validation is also critical, van 't Veer observed, before a test is used with patients.

Oversight of Genomic Tests

In order to ensure good quality control and regulatory oversight, genomic tests used in clinical trials should be required to obtain an investigational device exemption (IDE) from FDA, said van 't Veer, and in the case of companion diagnostics this should be included as part of the Investigational New Drug (IND) application. Institutional review boards (IRBs) also need guidance on how to review genomic tests. "There are large differences between IRBs of different institutions in how they review these tests. Some metrics—what they should look at—should be established." In cases of local hospital trials, where broader oversight is not available, entities should be established to review genomic tests for clinical trials. Meanwhile, FDA oversight of in vitro diagnostic tests "is working," according to van 't Veer. Postmarket surveillance and medical device reporting create much more standardized reporting around the use of these tests, which is important for patients.

Educational Needs for Decision Making

There is a great need for education about the clinical use and clinical impact of genomic tests. Many require the use of new technology by patients and physicians, making their assessment essential to facilitating proper use and understanding. Even for tests that are currently available, use is not 100 percent. Provision of more information over the Internet or through some other means could help move the field forward, van 't Veer said. For reimbursement agencies, cost-effectiveness studies and technology assessments which review logistical processes in hospitals should be included as part of their procedures for gaining information of clinical utility. van 't Veer also stressed that guidelines committees and regulatory bodies need to come together and harmonize their definitions of clinical utility, which currently vary from one group to another and between situations.

OVERCOMING OBSTACLES TO TEST DEVELOPMENT

Diagnostic expenditures account for only about 2 percent of health care costs in the United States, but are used to direct 70 percent of clinical decision making (West, 2011), said Russell Enns of Cepheid while speaking on behalf of Advamed Diagnostics. Molecular diagnostics in particular has been the fastest-growing sector of the diagnostics industry and it continues to grow at a faster pace than other areas of traditional laboratory medicine.

Enns discussed the three biggest obstacles that need to be overcome in the development and implementation of these tests.

Establishing Safety and Effectiveness

Novel technologies present great challenges for FDA's premarket review paradigm, said Enns. What is needed is a modernized, risk-based regulatory approach for all diagnostics that would support public health, encourage innovation, improve the transparency of the FDA decision process, and focus review resources on the products with the highest or most unknown risk.

Enns called particular attention to class II devices, where it has become more and more difficult to grandfather a device to pre-1976 standards. However, Enns has cleared 34 class II 510(k) molecular diagnostic devices through FDA. "My takeaway is that the FDA system does work," he said. "It has worked for me not only with infectious disease diagnostics, but also for cancer and genetic tests. I would say that it's been just as successful using the system in breast cancer and bladder cancer." However, the system needs refinements if test developers are to remain strong in the United States and continue to provide high-paying jobs for researchers, drug developers, and state-of-the-art manufacturing personnel.

In the European Union, the IVD Medical Devices Directive allows most products to be introduced into the market through the self-declaration of a compliance process with standards issued by the International Organization for Standardization. "This system has been in place for about 10 years and has served Europe well," said Enns. "Perhaps Congress can take a closer look at the EU system to better assess global competition while maintaining product safety and effectiveness standards." However, Enns cautioned that drug development standards should not be overlaid onto diagnostics products.

Establishing the Value of Diagnostic Tests

Establishing the medical necessity or the value added by a diagnostic test would help overcome what Enns termed "the largest obstacle to [the] successful introduction of new molecular diagnostic tests and platforms"—reimbursement coverage. Payment reform is needed to recognize the value of advanced medical diagnostic tests, their impact on treatment and management decisions for patients, and the resources needed to develop and validate tests. The current reimbursement rates for diagnostic tests are based on an outdated, flawed fee schedule that has not even kept pace with inflation, according to Enns. Inadequate payment affects innovation, as well as patient access to new tests. "It's much simpler to make major medical

discoveries and advances in medical diagnostics than it is to obtain reasonable and timely reimbursement in coverage decisions." A legislative solution to address payment reform may be needed to ensure the development of "reliable and transparent procedures open to public review and debate by all stakeholders," said Enns.

Establishing Performance Standards

Reliable and accurate performance standards and practice guidelines for new genomic tests need to be established, stressed Enns. Patients deserve standardized, consistent test results regardless of where or when tests are performed. "Patients need to be able to go to any cancer institute in this country and [have] a blood sample drawn for an accurate and reliable test." Many organizations develop performance standards for such attributes as analytical sensitivity and specificity, interference, precision, reproducibility, and clinical sensitivity and specificity. Enns described in particular the Clinical and Laboratory Standards Institute, where he has volunteered for more than 25 years. Over the past two decades, the institute has developed 16 different molecular standards for laboratory medicine, many of which have been officially recognized by FDA as performance standards.

Enns concluded by saying that the United States can keep doing what it has been doing or it can keep up with changes in laboratory medicine by modulating regulatory requirements and professional practice standards. "Since the United States now represents less than 5 percent of the world's population, we can stick our proverbial heads in the sand and watch the world pass us by. [But] there's no need for that to happen. . . . Let's stay competitive, let's continue to solve disease problems, and let's further improve the quality of life and the length of productive lives by working together on solutions to these obstacles."

PRINCIPLES FOR SUCCESS

Cancer kills more than a half-million people in the United States each year (Siegel et al., 2012), yet it is often still treated with products of limited clinical utility and a one-size-fits-all approach, said Steven Shak of Genomic Health. As a result, "we punish the many to benefit the few." For example, the classic B-20 study of the National Surgical Adjuvant Breast and Bowel Project, which looked at chemotherapy plus tamoxifen versus tamoxifen alone in the treatment of patients with auxiliary lymph node–negative, estrogen receptor–positive breast cancer, showed that only 4 out of every 100 women benefit from chemotherapy (Figure 3-1) (Fisher et al., 1997).

At the end of the 20th century, a new generation of technologies was developed which was used to sequence the human genome. These tech-

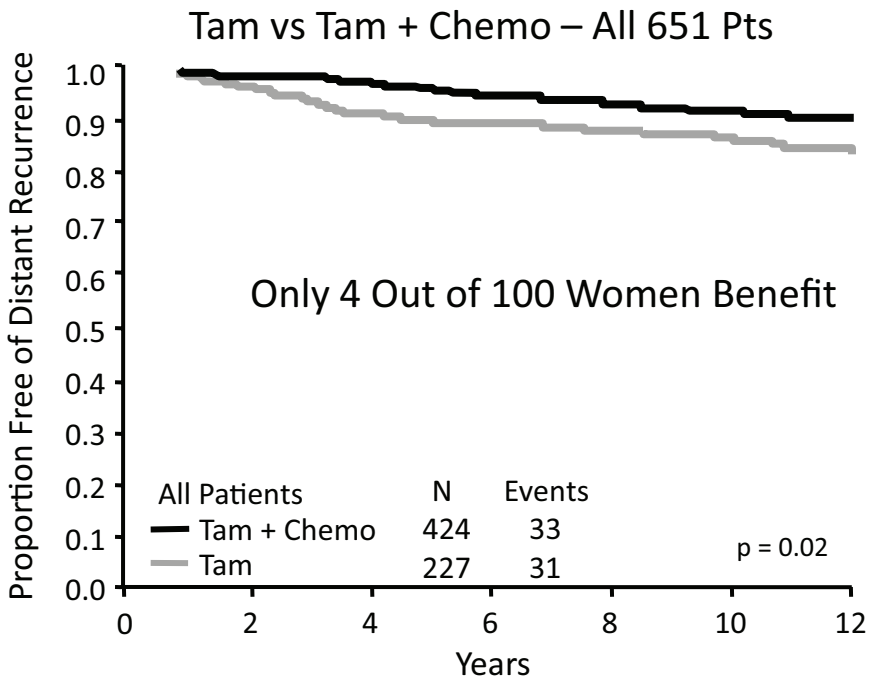

FIGURE 3-1 Little significant benefit is seen from use of chemotherapy in addition to tamoxifen treatment for patients with lymph node–negative, estrogen receptor–positive breast cancer.
NOTE: Tam, tamoxifen; Chemo, chemotherapy.
SOURCE: As adapted by Shak from Fisher et al., 1997.

niques have revealed the underlying complex biological systems involved in cancer and suggested many new drug candidates. However, efforts to codevelop drugs and diagnostics have not been very productive, Shak observed, with just a few exceptions. The directed use of trastuzumab for metastatic breast cancer patients that test positive for HER2 (Slamon et al., 2001) has saved tens of thousands of lives, but other tests linked to biologic therapies have not emerged from clinical evaluation, said Shak.

Oncotype DX

Genomic Health initiated an effort in 2000 to develop and commercialize molecular diagnostic tests that would empower cancer patients and their physicians to be able to select the right treatment based on the underlying biology and on reliable evidence of clinical utility. "That was a tall goal," said Shak, but the company's Oncotype DX breast cancer assay, which was

developed as an LDT under the provisions of CLIA, has now been clinically validated in 13 studies involving more than 4,000 patients and it has been used in more than a quarter million patients since becoming available in 2004. The test is reimbursed in the United States by Medicare and all the major payers, is provided for patients in more than 65 countries, and has been incorporated in published treatment guidelines.

Shak described several key principles on which success in the biomarker field is based. First, a test needs to deliver what patients, physicians, regulators, and payers need and this has to be considered at the very beginning prior to development. Most important, it should be "fit to purpose," with evidence relevant to that specific purpose. It should give consistent results across multiple, well-designed studies. And the test must be shown to have value beyond traditional measures to all stakeholders. To do that, the test needs to be compared head-to-head with what has been used traditionally, so that comparative effectiveness is built into the strategy from the beginning. "The short version of this is that you need to bring the rigor of drug development to the development of diagnostics, but also fit for purpose," said Shak.

Shak laid out a roadmap to establish clinical utility that consists of the following steps:

- Definition of purpose
- Technical feasibility
- Development studies
- Analytical methods finalization
- Analytical methods finalization and validation
- Clinical validation studies, including comparative effectiveness
- Treatment decision studies
- Health economic analysis

Shak pointed out that diagnostics can have a major impact on treatment decisions. Seven studies of the Oncotype DX recurrence score in 912 patients showed that treatment decisions changed 30 percent of the time compared with what would have been done without the recurrence score. This is one way of addressing the question asked by Hayes: Is a test being used appropriately?

The second principle Shak listed is that technical innovation needs to be brought to standardized implementation. This requires that all assay methods and procedures be defined prior to clinical validation studies in such areas as specimen eligibility, reagent qualification, instrument validation, controls and calibrators, and linearity, precision, and reproducibility.

CLIA is built on regulations and principles of laboratory medicine "that have been in existence now for decades and really work," said Shak.

He cited the CLIA-certified reference laboratory process accredited by the College of American Pathologists (CAP) for the 21-gene recurrence score, which uses more than 150 standard operating procedures, 94 forms, and an information technology system that looks at every reagent and ensures that the appropriate quality control is used. "An inspector can come into the Genomic Health [laboratory]—and we've had 10 inspections—and say, 'On March 7 we want you to look at the tenth test that you did that day and then pull out the quality control metrics for every reagent that was used in that particular case.' We monitor that and can do that."

The third and final principle Shak listed is that the development of diagnostic tests requires collaborations, clinical research funding, and the skills, processes, resources, and incentives to do it right. "Sometimes the hardest thing isn't the technology; it's people."

One particular obstacle Shak mentioned is the potential need to address all of the payers individually, of which there may be 100 or more in the United States and abroad. Innovative systems need to be developed by payers to gauge the value of the diagnostic in their own system. He described a method implemented by Clalit, which is the largest payer in Israel, to document the value of Oncotype Dx use. Clalit created a simple form that physicians filled out in order to get access to the test, in which they indicated what they would have done without it. "Since they're the payer, they could collect what was done. They could rapidly document for themselves the impact of the test in their clinical practice." Another innovative system implemented by CareFirst and Highmark was to pilot a program which provided greater reimbursement at a higher rate for the appropriate use of Oncotype Dx. "We need to be innovative in the way that we think about capturing data in clinical practice . . . and providing incentives around it," said Shak.

He also listed obstacles and potential solutions to the development of diagnostic tests, some of which were also described by other speakers:

- There is a knowledge and experience gap among those working in and assessing this new field which needs to be closed through continued education.
- Current incentives have the effect of encouraging individual rather than team science. Leadership, teamwork, and collaboration needs to be incentivized and rewarded.
- Reimbursement is uncertain, which points to the continued need to move to pricing based on value.
- Regulation is uncertain, which points to the need for regulations that are fit to purpose and suitable for continued rapid introductions of new and improved tests.

Shak concluded by observing that his company has been working in recent years on next-generation sequencing technologies that have made it possible to investigate not just candidate genes but the entire transcriptome. "I never would have dreamed in my lifetime that it's now possible to see . . . over 50 million reads from a single sample. How do we analyze that data? What are the bioinformatics? How do we apply and harness this technology? The principles that we're talking about here are what is needed to make it possible to actually bring these advances in a responsible way to patients."

4

Patients

Important Points Highlighted by the Speaker

- Varying claims about the usefulness of genomic tests can be extremely confusing to patients.
- People with cancer need ways to get their questions answered by health care providers at the point of clinical decision making.
- Severe illnesses may require different rules and guidelines than less severe illnesses.
- Conversations regarding the development of new diagnostic tests should begin with the needs of the patient, not with how to get reimbursed for a test or treatment.

The National Coalition for Cancer Survivorship (NCCS) was founded in 1986 to advocate for quality cancer care. It is survivor led—its bylaws require that a majority of the board of directors have a personal cancer diagnosis—and it has created and promoted the language of "cancer survivorship" as an alternative to "patient" or "victim."

Mark Gorman of NCCS noted that cancer survivors have rising expectations with respect to genomic and other tests. They see these technologies as potentially guiding them toward more effective treatment and reducing the time they spend on ineffective therapies. However, they do not under-

stand the complexity of genomic tests and there is confusion about their true usefulness.

POLICY POSITIONS

NCCS has adopted several specific positions on matters involving genomic diagnostic tests. It supports vigorous FDA oversight of these tests but with the recognition that a clearly defined regulatory pathway is needed, especially for companion diagnostics. The main concern is that uncertainty in the current regulatory environment will lead to inefficiency and slow progress. NCCS is also very concerned about finding ways for people with cancer to get their questions answered by health care providers at the point of clinical decision making. Cancer treatment planning is a very complex process that is becoming even more complex. People need information and time to understand the implications of the choices they are offered.

ISSUES OF CONCERN

Cancer care is at the forefront of the development and use of genomic diagnostic technologies, said Gorman. As a cancer survivor, he wants these diagnostic tests to reduce uncertainty and help in the management of resources. This requires coordinated care and a full understanding of the use and implications of these tests by care providers. Many people seek out second opinions, and it is not uncommon for the pathologist at a second cancer center to have a different conclusion from the initial diagnosis. Questions then arise as to whether the pathology has been correctly interpreted and whether a patient might have to face repeat tests and costs. Without trust in the entire care team to properly advise a patient's treatment, this may prove to be a significant obstacle for moving these new technologies forward.

Severe illnesses may be different from less threatening illnesses with regard to testing and may require different rules, Gorman pointed out.

If investigational interventions begin to enter clinical practice, the subject of that intervention should know that information, Gorman said. This knowledge will temper expectations and may affect choices. However, if this is a pathway that is used, then the interventions should be done in a manner that will generate evidence. Collection of evidence does not need to be through a randomized controlled trial, but it should be systematic, he said. Gorman warned, though, that use of the investigational system needs to be properly vetted to avoid setbacks that can undermine patient trust, harm the field, and delay progress. Third-party oversight may be useful in this regard.

Finally, Gorman pointed out that cancer survivors have become very frustrated with conversations about how to bring the best care models and goals to widespread use that begin with the question, How can it be paid for? "Personally, I prefer a dialogue that begins with the question, 'What do patients and cancer survivors need?' Then we move on to the questions of how can incentives be aligned to realize it."

5

Payers

Important Points Highlighted by the Individual Speakers

- A progressive or adaptive regulatory and reimbursement framework, in which initial approval is conditional upon further study, has many advantages over a binary approval model.
- The full range of stakeholders should collaborate to develop standards defining evidentiary thresholds.
- Critical reasoning medicine can support coverage decisions when the data to make these decisions are incomplete.

In a session featuring individuals with experience in health care payments, speakers discussed the issues that arise in making coverage and reimbursement decisions. A repeated theme of their presentations was that binary decisions to approve or disapprove a genomic diagnostic test are not in keeping with the nature of the evidence. A better approach is to make decisions in stages as more evidence becomes available, suggested participants. Rigorous standards can help in implementing these kinds of progressive approval and reimbursement systems.

PROGRESSIVE REGULATION AND REIMBURSEMENT

There is an inherent tension between level of certainty about risks and benefits and early access to new technologies or innovation, said Sean

Tunis of the Center for Medical Technology Policy. The higher the level of assurance needed that a patient will benefit from a genomic technology, the greater the burden on gaining the evidence to provide that certainty, which puts downward pressure on innovation. Similarly, the more emphasis that is placed on reducing health care costs, the greater the downward pressure on economic growth and jobs. "It's not intuitively obvious what the optimal balance of innovation and certainty is that maximizes public health over time," said Tunis.

Tunis focused on two related barriers to the development of clinically useful genomic diagnostic tests:

- Regulatory and reimbursement decisions rely on a binary model of approval.
- Evidentiary thresholds for regulatory and reimbursement decisions are poorly defined.

Today, regulatory and reimbursement decisions are made as if there were a "magic point" at which suddenly something is true where previously it was false, said Tunis. "We pretend that evidence is kind of an ordinal property as opposed to a continuous function, but that's obviously not true."

A much better model, said Tunis, is a progressive or adaptive regulatory and reimbursement framework. In this case, approval or disapproval decisions are not made at a particular time; rather, they are made progressively over time. Coverage with evidence development (CED) and managed entry schemes are examples of such models for reimbursement with initial approval conditional upon further study. Accelerated approval would be an example of a progressive regulatory model. "Having single yes/no decisions over time is just too crude an approach," said Tunis. "If we're going to solve this problem with technologies generally, and certainly with diagnostics, we need to think about our regulatory decision making in a way that's more compatible with the accumulation of knowledge and the reduction of uncertainty over time."

Decision making today is not predictable due to a lack of clarity regarding the regulatory and reimbursement pathways, Tunis said, reiterating Siegel's remarks. What is needed is a collaboration involving regulators, payers, clinicians, patients, and other stakeholders to define what the evidentiary thresholds should be. This cannot be done at a generic level but rather must be fit for purpose. The evidentiary threshold will need to be defined in a way that is specific to indications and therapies. "Our current regulatory or reimbursement policy framework is not aligned with the nature of evidence and the accumulation of knowledge over time. Until it is, we're going to have a very inefficient system," said Tunis.

Importantly, no new regulatory or statutory authority is needed to take these steps, according to Tunis. FDA and CMS have implemented progressive systems and could institute similar systems in the future.

Effectiveness and Guidance

The Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) stated that "information on clinical utility is critical for managing patients, developing professional guidelines, and making coverage decisions" (SACGHS, 2008). This group recommended that the Department of Health and Human Services create "a public-private entity of stakeholders to . . . establish evidentiary standards and levels of certainty required for different situations."

Tunis briefly described some work being done at his center that follows up on these recommendations. He and his colleagues are creating documents called effectiveness guidance documents that are analogous to FDA's regulatory guidance documents. However, instead of describing how to design studies in specific therapeutic areas to meet regulatory requirements, the effectiveness guidance documents reflect the information needs of patients, clinicians, and payers. Such guidance is designed to be complementary to regulatory guidance.

The development of effectiveness guidance documents starts with systematic reviews that identify deficiencies in the existing evidence base, Tunis said. Content experts generate initial draft recommendations, which are refined by a technical working group. The revised recommendations are discussed at a multidisciplinary methods symposium, which brings together various stakeholders for public comment, after which the recommendations are finalized and posted. As a specific example, Tunis cited the following draft recommendation: "Valid outcomes or surrogates for breast cancer prognosis include distant recurrence at 5 or 10 years, disease-free survival, disease-specific mortality, and overall survival." Whether this strikes the proper balance between innovation and certainty would have to be determined, but the appropriate response is to adjust the threshold and not give up on the process of coming to a consensus.

"We can't move forward without some kind of mechanism to get everybody on the same page in terms of the minimally acceptable level of certainty for making these regulatory and reimbursement decisions," said Tunis. "It's not a property of evidence. It's a property of collective social judgment, so you need a collective social process to define what these thresholds are."

THE NEED FOR STANDARDS

Louis Hochheiser of Humana said that standards for determining what should and should not be covered by insurance companies would greatly benefit their decision-making process. "It's an enormous task. We have such great difficulty."

Humana provides coverage for 11.5 million people and tries to create policies to cover them in a rational way. It puts patients and improving health outcomes as its primary focus, said Hochheiser. This requires both education for providers and the public and the pursuit of cost-effectiveness. Humana preauthorizes its genomic tests and, Hochheiser said, finds that 20 to 25 percent of the ordered tests are inappropriately ordered. This is a huge issue that needs to be addressed.

Decisions need to reflect acceptance from all stakeholders, including physicians, patients, diagnostic companies, payers, regulators, pharmaceutical companies, and policy makers. Humana wants to be part of that decision making, said Hochheiser. "We don't want to drive it. In fact, we find ourselves driving it now when we don't want to be driving. But we do want to be in the room to talk about it and give a perspective of what it's like to be responsible for a large portion of our population."

Clarifying Expectations Through Standards

CMS and other payers need to clarify standards around developing technologies, Hochheiser said. This would clarify criteria for coverage, both for payers and for the developers of tests. Today, each payer has teams of people who are evaluating new technologies in order to enable decisions regarding coverage. "We are spending millions of dollars a year [on evaluation] that could be going into developing appropriate testing [because] we don't have a system, we don't have a set of standards to go by."

Standards would allow for more rapid deployment of genomic tests rather than waiting for peer-reviewed publications. They also would allow payers to make consistent decisions and would permit uniformity between CMS policy and that of commercial payers. "4.5 million of our 11.5 million [covered individuals] are CMS recipients . . . and yet we can have different rules," said Hochheiser.

A system of standards should allow for continuing validation over time. For example, Humana was the first adopter of Oncotype DX in the United States, but it has not stopped at just the coverage decision. The company has continued to study the population that receives the test. It has found that 15 percent of the women with a low recurrence score, indicating negligible benefit from chemotherapy, choose to have it anyway. Half of the people with recurrence scores in the middle choose to have chemotherapy

and the other half choose not to. Of the women with a high recurrence score, 15 percent choose not to have chemotherapy; that population needs to be studied as well, said Hochheiser.

Humana shares the responsibility of clarifying the value of clinical technologies. It has a population of people that it can follow over time, and it is working with researchers to study the effects of interventions in this population. The company is willing to consider new coverage models, such as CED, when long-term studies are not practical. They are also willing to meet with test developers and participate in the development process. At the same time, it needs to have a reasonable price point. "If Humana . . . covers every test, we soon will have a product that we can't sell competitively with the other insurers, which is why we need a level playing field where everybody knows that everybody is playing on that same field."

Humana also is interested in working collaboratively to minimize errors. When a provider seeks a preauthorization, education materials are available for that person. The company also works with an outside business to provide genetic counselors.

"It's absolute need for standards, collaboration at multiple levels, [and a] coordinated approach through all the different stakeholders. [Genomic diagnostic tests] have too much potential impact for us not to do something about it and do it now," said Hochheiser.

Capital Investment

Finally, Hochheiser asked whether venture capital is the best model for developing genomic tests that can make a huge difference in the health of patients. Health care reform, he pointed out, is taxing all insurers on their premiums. "Shouldn't some of that money be directed toward the innovations that we need in health care to make progress?"

FROM EVIDENCE-BASED TO CRITICAL REASONING MEDICINE

Bruce Quinn of Foley Hoag provided a more theoretical perspective on the utility and adoption of genomic tests. Evidence-based medicine, as it is traditionally approached, can generate anomalies, he said. For example, a 2005 report by the U.S. Preventive Services Task Force (USPSTF) labels the association between mutations in the BRCA gene and breast cancer only "fair," said Quinn, despite significant research showing that patients who harbor BRCA mutations are at an increased risk of developing cancer (USPSTF, 2005). But because there are no randomized controlled trials (RCTs) of BRCA mutations, evidence of a causal relationship is not strong.

RCTs are designed to distinguish between correlation and causation, Quinn said. For example, high troponin levels are highly correlated with

having a heart attack (Thygesen et al., 2010), but giving troponin to people does not cause a heart attack, according to Quinn. Diagnostic tests, for their part, are useful because they indicate a reliable correlation.

Analytical validity, clinical validity, and clinical utility have limited usefulness, Quinn said. He used a book as an analogy. At one level, a book consists of ink, paper, and glue. At the next level, it consists of words, grammar, and a language. At the next level, it has content, meaning, and some measure of usefulness. But the usefulness of a book cannot be determined by studying its ink, paper, and glue. In the same way, a gene test with lower analytic validity may have a better correlation to a clinical outcome than another test for the same gene with higher analytic validity. The same is true for clinical validity, said Quinn, citing the differences in usefulness of hypothetically similar results between PSA testing and use of the Oncotype DX assay in predicting cancer recurrence. There is only a distant relationship between analytic validity, clinical validity, and clinical utility.

Tests often transform a question that cannot be answered into a question that can be answered, said Quinn. For example, the question "do we need to switch your HIV drug" is transformed to "is your HIV RNA count rising?" The key is the correlation between the answer the test provides and the question that needs to be answered.

There are two kinds of true statements, Quinn observed. The first are statements about things, like this is a rock or you have leukemia. The second are statements about relationships, like there are 10 dimes in a dollar or high troponin levels are associated with heart attacks. Clinical decision making deals with both kinds of statements. There are general medical rules consisting of principles, facts, and conclusions drawn from evidence and there are specific statements about a patient. Evidence-based medicine provides the backing for certain conclusions. The problem, said Quinn, is that medical science is very hard and requires considerable thought and expertise. Some evidence-based medicine may not add value when it is done in an unthinking or brute-force way.

An alternative model that Quinn mentioned is critical reasoning medicine, which combines the ideas of "we can believe this" with "we should do this." Specific patient facts are combined with clinical rules and knowledge. In turn, this reasoning can be used to support coverage decisions, which separately take into account funds, priorities, and available alternatives, even if complete data are never available when a coverage decision is made.

6

Regulation, Reimbursement, and Public Health

Important Points Highlighted by the Individual Speakers

- The lack of a coherent oversight system could create a chasm between the use of genomic diagnostic tests and improved health.
- Collaboration among and within federal agencies could ease some of the limitations of the current regulatory system.
- Agencies have been experimenting with progressive approval as one way to provide more regulatory and reimbursement flexibility.
- A public health approach to genomic diagnostic tests would evaluate their utility to reach evidence-based recommendations and then evaluate their impacts at the population level.

Government has the responsibility to protect the public health and safety, yet it does so with a patchwork of laws and regulations and must base its decisions on evidence that is poorly developed in many areas. Three speakers discussed the approaches taken by the Centers for Disease Control and Prevention (CDC), FDA, and CMS. All acknowledged the many difficulties of overseeing genomic diagnostic tests while pointing toward promising innovations.

A 21ST-CENTURY OVERSIGHT SYSTEM

Major components of 21st-century medicine lack suitable oversight mechanisms, said Muin Khoury of CDC. Huge quantities of data have become available and much more is on the way, yet in many areas there remains an evidence gap between interventions and outcomes. Stakeholders have different perspectives on this evidence gap. While some may feel that sufficient evidence exists to meet their needs, others may not. The confusion generated by the lack of oversight creates less than optimal awareness and knowledge among consumers, providers, and systems.

In the area of genomic diagnostic tests, the lack of coherent oversight creates what Khoury termed "premature translation." Genomic tests move from the bench to the bedside quickly with no strings attached because they go through the LDT route. "Spit in a test tube and you get results." However, there remains a chasm between the use of these tests and improved health, which Khoury described as the "lost in translation" gap. Products seep through the translation process, some good and some bad, while information about their effectiveness is often lacking.

Khoury pointed to the need to develop what he called a public health approach to genetics (Figure 6-1). He admitted that the term is something of an oxymoron, since genetics is about personalized medicine and public

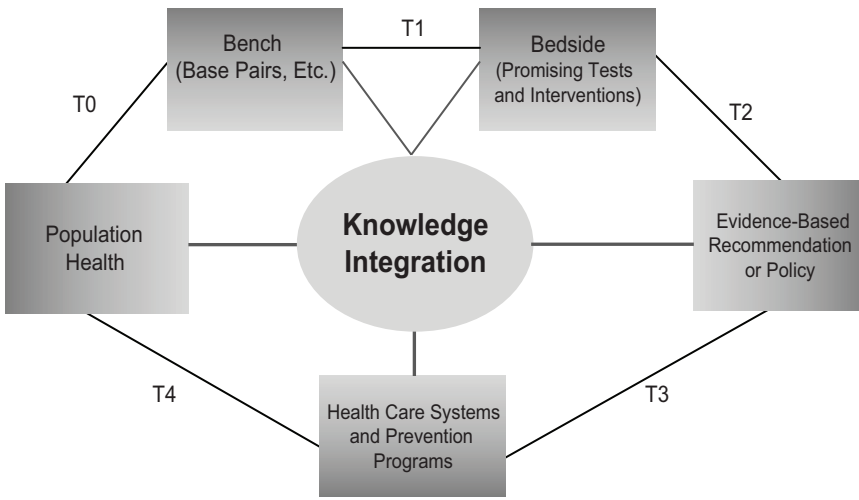

FIGURE 6-1 The public health genomics model allows for a balance of the translational research (T0 through T4) needed to convert discoveries into better health. SOURCE: Khoury, IOM workshop presentation on November 15, 2011.

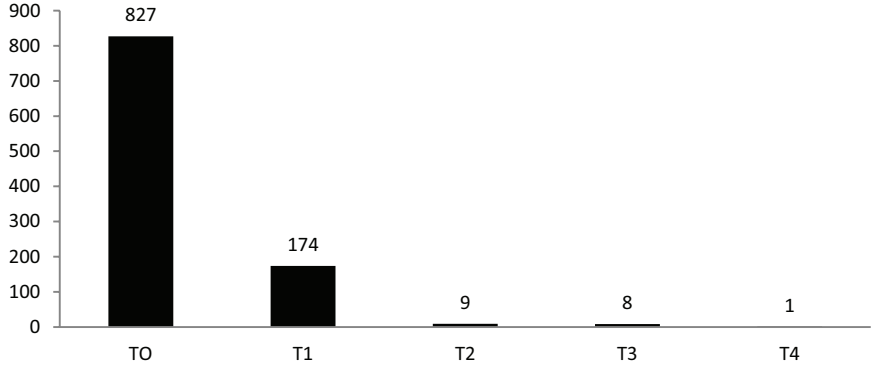

FIGURE 6-2 An analysis of 2007 National Cancer Institute cancer genetics and genomics grants indicates very few supported research studies in later translational stages, with the majority falling into discovery or early translation.
SOURCE: Schully et al., 2011.

health is about populations. But combining the two would benefit both endeavors through the development of a robust translational research enterprise that not only gets tests from bench to the bedside but evaluates their utility to reach evidence-based recommendations and then evaluates their impacts at the population level.

The current system does not fund this kind of research though, Khoury observed. According to a recent portfolio analysis of cancer genetics and genomic research at the National Cancer Institute, most funding goes for discovery or early translation (Figure 6-2). Less than 2 percent of funding is focused on clinical utility or later stages in the translation process (Schully et al., 2011). As a result, different stakeholders use different evidentiary frameworks to decide on the value of tests.

Potential Solutions

The way to solve this problem, according to Khoury, is through a 21st-century oversight system. For example, one such system would be the one suggested by Hayes, in which LDTs are eliminated and FDA oversees the approval of all tests. Another potential solution is greatly increased public and private funding for research focused on clinical utility and beyond. These may or may not be the right solutions "but at least [they are] outside the box."

A third potential solution is a knowledge integration enterprise that would involve both information brokering and knowledge synthesis. One approach to knowledge integration has been pioneered by CDC's Evalua-

tion of Genomic Applications in Practice and Prevention (EGAPP) group. EGAPP is an independent multidisciplinary working group that has been a "lightning rod" for discussion, according to Khoury, since it was formed in 2005. It has developed methods and outcomes processes, has conducted systematic reviews, has pointed to evidence gaps, and is beginning to tackle evidentiary standards for whole genome sequencing. "What EGAPP has tried to do is create analytical frameworks that allow data to be gathered across multiple platforms from observational studies to clinical trials," Khoury said.

A second initiative launched by CDC and other public and private organizations in 2009 is the Genomic Applications Practice and Prevention Network (GAPPNet), which is designed to put stakeholders in the same room and connect them to data. The first objective of GAPPNet, according to Khoury, is to build the necessary information from discovery through health impacts. The second is to deal with stakeholder forces that affect translation by letting them talk through issues. "Maybe they will or will not reach consensus, but they need to be aided or helped by that oversight system."

Overcoming Obstacles to Progress

The most important obstacle to the establishment of a 21st-century oversight system, said Khoury, is a lack of incentives. There are few incentives for public or private funding of research beyond the discovery phase, for knowledge synthesis and stakeholder convening, or for public and provider education.

To overcome these obstacles, it is necessary to start at the top. Pilot oversight "experiments" need to be developed and applied to deal with insufficient evidence, said Khoury. Public and private initiatives could come together to fund the generation of clinical utility evidence. The new Patient-Centered Outcomes Research Institute established by the Patient Protection and Affordable Care Act could potentially investigate these issues if it had sufficient funding. Small experiments by FDA, CMS, and the Agency for Healthcare Research and Quality (AHRQ) have moved in the right direction, but these need to be coordinated and expanded. As an example of a pilot project that Khoury initiated with funding from the American Recovery and Reinvestment Act of 2009, seven groups were funded to conduct comparative effectiveness research in genomics and personalized medicine and to develop a collaborative road map. Much of this work is about to be released. In addition, EGAPP continues to explore new methods and approaches. What is needed, said Khoury, is "a stakeholder-driven knowledge integration enterprise that explores novel methods of synthesis, decision analysis, and modeling."

FDA REVIEW

The 1976 Medical Device Amendments defined in vitro diagnostics as "medical devices" and established a risk-based regulatory paradigm for their oversight. The safety standard is that "there is reasonable assurance . . . that the probable benefits . . . outweigh any probable risks" [21 CFR 860.7(d)(1)]. The effectiveness standard is that "there is reasonable assurance that . . . the use of the device . . . will provide clinically significant results" [21 CFR 860.7(e)(1)].

The risk-based strategy has "strengths and weaknesses," said Alberto Gutierrez of FDA. The standards are similar to those for drugs but they also differ in significant ways. For example, a premarket approval application (PMA) for a diagnostic is thought of by individuals to be similar to a New Drug Application in many ways, but controlled clinical trials are rarely submitted as the evidence base. Half of the devices that are currently on the market were not reviewed by FDA prior to their release and for another 40 percent, they just have to be similar to an already existing device. Only very high-risk devices require a PMA submission.

Gutierrez emphasized that the regulations extend from premarket to postmarket to compliance. In the premarket, industry provides the evidence and FDA reviews and clears or approves the device. In the postmarket, industry has the responsibility and FDA monitors and provides guidance. With compliance, FDA monitors companies to make sure that they comply with the law and regulations.

Progressive Approval

Gutierrez briefly discussed the idea of accepting a lower level of evidence premarket while relying on postmarket studies to gather additional evidence. FDA has done that in some cases, partly because the performance of a diagnostic is closely tied to the population in which it is used. Sometimes, good evidence for safety and effectiveness exists in one population but not another and, in this case, FDA will clear or approve the test but require postmarket data to be collected. For example, FDA cleared a test used in women with a pelvic mass that helps determine whether the mass should be removed by a gynecologist or by an oncologist,[1] but it also required postmarket study to gather additional data on premenopausal women, for whom fewer data were available than for postmenopausal women.

[1] Ovarian Adnexal Mass Assessment Score Test System; see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm237299.htm.

Elements of Review

FDA evaluates analytic validity and clinical validity in its reviews, but Gutierrez stressed that the major factor that FDA considers is actually the intended use of a device, which does not necessarily preclude an evaluation of clinical utility. Some uses are very broad, in which case clinical utility is generally hard to assess, whereas others are very specific, in which case clinical utility is very important, said Gutierrez. If the claim behind an intended use is one of clinical utility, then that needs to be demonstrated. FDA also tries to be very transparent in its reviews, both consulting with expert panels when necessary and publishing the basis of its clearances.

Many groups, including FDA, recognize that there are regulatory gaps regarding LDTs, Gutierrez said, though they do not necessarily agree on how to solve these problems. Laboratories rightly observe that they are governed by CLIA. They also observe that clinical validity emerges from the published scientific literature, so that peer review is essential. However, "when the devices are very difficult to replicate, we've seen peer review and the literature not be a good form of regulation."

A major problem with LDTs is that they have created confusion regarding the rules of the road from test development to research. How can patients be protected during postmarket research? How can it be determined that a test has failed, and what happens when a test has failed? "In general, this is an area we need to fix," Gutierrez said.

Barriers to Successful Test Development

Gutierrez acknowledged the many problems raised by other presenters: diagnostic tests may not provide a sufficient return on investment; a lack of regulatory clarity can introduce uncertainty into the development of tests; many tests do not have much evidence regarding their utility; and LDTs lack standards and can be difficult to integrate into medical practice. These problems do not have easy solutions, said Gutierrez. Collaboration between FDA and CMS could help, and a pilot program between the two agencies is testing this approach. Collaboration within FDA also can be important. Much remains to be done in this area, but some of the collaborations within the agency are working well, according to Gutierrez.

FDA also has collaborated for many years with standards-setting bodies such as the National Institute for Standards and Technology. However, these efforts have been piecemeal and depend largely on finding someone who is willing to collaborate and the money to enable the collaboration. "It's not an approach that is well thought out or that people can actually plan on in a very straightforward way."

Putting the Patient First

The broader obstacles are that the health care system is "fairly chaotic," with different people and institutions pulling in different ways. Financial interests favor the status quo, so change generally has to come from the political arena. However, this setting may not be optimal for discussions to identify and fix these issues, said Gutierrez.

Gutierrez concluded by pointing out that the focus should remain on the needs of patients. "We all need to figure out what is our responsibility in making this work." People may need to take actions that are not in their best interest but are necessary to improve the overall system. "We all need to pull together, otherwise it's not going to happen."

COVERAGE BY CMS

The task of a test developer is to make investors, regulators, and users more confident about their test, said Louis Jacques of CMS. This task is made much easier when certain conditions apply.

First, it is easier when clear and consistent scientific evidence supports clinical utility, though this is a difficult condition to achieve, said Jacques. It also is easier when the risks of "medical misadventures" are known, measurable, and acknowledged. For instance, how easy is it for a physician to know that a genomic test result is mistaken or was not run on the proper sample? In addition, managing a perceived risk may affect an unknown or unrecognized risk. "If we arguably knew how to reduce our risk of heart disease by doing certain things, taking certain medications, how do we know that we haven't increased our risk of neoplasm?"

Physicians need to consistently use the test where it fits in an overall management scheme, though this, too, is often difficult in practice. Even if CMS covered and paid for all genetic tests, they would probably be used chaotically in practice, Jacques said.

A standard nomenclature and taxonomy can increase confidence in the utility of a test. Having the relevant components consistently and precisely identified in a claims stream for a test would allow for easier evaluation. Currently, because of the use of stacking codes, Medicare already pays for many genetic tests, said Jacques, but "we're not doing it in an intentioned or well-reasoned manner." Rather, the test is part of a claims stream and is reimbursed unless someone prevents it.

Finally, a genomic test generates more confidence when there is agreement on its value. The evidence base is still largely immature, said Jacques. It stops well short of clinical utility, and at times short of analytic validity. Also, the evidence is not holistic, in that it is challenged to incorporate particular factors. For example, what is known about particular patient sub-

groups? "Is the relevance of a particular biomarker or a particular genetic test the same thing when you're 70 years old and you've already expressed certain diseases as it is when you're much younger?"

Factors in Coverage Decisions

Age is also a factor in assessing the value of genetic tests. Young people have a lifetime to manage their risks but may have little personal incentive to do so. Genomic testing may not be as relevant for a person who joins the Medicare program at 65 as it is when he or she is 2 years old, said Jacques. "Why shouldn't people arrive . . . in the Medicare program with whatever predictive genetic factors that may be brought to bear, in fact, already done?"

Another factor Jacques cited is that genetic tests can have multiple platforms, multiple vendors, and multiple indications. In such a setting, reference standards can be critical. Several years ago, Jacques attended a meeting in which test developers could not agree on the definition of the colors used in their test. "I told them at that meeting that they had absolutely no chance of Medicare reimbursement unless they could at least agree on standards," he said. "Sure enough, by the next year they had collaborated with NIST and actually developed standards." Evaluating a product without knowing the starting reference point is a real difficulty, said Jacques.

Finally, a major challenge within CMS, as with FDA, is that payment decisions are binary. Statutes dictate how CMS must pay for covered health care practices. For example, congressional mandates delineate coverage for screening tests versus diagnostic tests, with screening tests tied to the findings of the USPSTF recommendations.

In contemplating the evaluation of tests, Jacques wondered if granting full reimbursement for a covered test would act as a disincentive to the development of further evidence. Jacques questioned whether it might make sense to pay initially at a lower level—say at 75 percent. Then, as the evidence base matured and if evidence demonstrated clinical benefit, a payment premium could be awarded—say 135 percent. Such a system could support future innovation and the development of "the next big thing."

Innovation in Review

Several initiatives have been developed to enable collaboration between CMS and FDA, including the parallel review process and CMS representation on FDA's Council for Medical Device Innovation. CMS has been open to accompanying test developers and others if they choose to meet with FDA for initial feedback, Jacques said.

CMS also has been doing coverage with evidence development for sev-

eral years, though it recently sought new public input on its CED guidance document. "I'm seeing big players in industry . . . make public comments that CED is good for innovation," he said. Jacques also would like to see CED have greater breadth and flexibility so that not every new molecular indicator and LDT needs to be reviewed.

Medicare still has considerable local authority, Jacques pointed out, and local decisions do not necessarily apply nationwide. More collaborative review processes could help create greater nationwide consistency.

7

Discussion of Major Proposals

During discussions throughout the workshop, participants commented on the major proposals made by speakers (see Box 7-1). Those discussions are consolidated in this chapter as a way of summarizing the major themes of the workshop.

ELIMINATING THE LDT PATHWAY

Throughout the workshop, participants returned to Hayes' proposal that the LDT pathway be eliminated and all genomic diagnostic tests be reviewed and approved by FDA.

Several participants pointed to the value of the LDT pathway. For example, Conti observed that in some areas of medicine, especially where good publications are available, it may cost far less to develop an LDT than the numbers Siegel cited in her presentation. CLIA provides much value to areas of medical practice, such as infectious diseases, endocrinology, or neurology, that are willing to accept published research as good evidence of treatment improvement. "You can do that very efficiently with respect to capital. Small laboratories can bring up LDTs without having to raise millions of dollars."

Shak said that once a test developer has been successful with an LDT, the developers of that test are eager to produce new tests because of the beneficial effects they have on the lives of patients. This is one of the reasons why companies continue to invest in research and development, even when a final test is years away and reimbursement is uncertain. Only a fraction

BOX 7-1
Major Proposals Made by Individual Speakers

- Eliminate laboratory developed tests and have all genomic diagnostic tests undergo FDA review and approval. (Hayes)
- Base FDA approval on analytical validity and clinical utility, not clinical validity and intended use. (Hayes)
- Consolidate the review of all oncologic products within a single FDA office. (Hayes)
- Base reimbursement on the value of a genomic diagnostic test to patients, payers, and society. (Hayes)
- Clarify the regulatory and reimbursement pathways for genomic test development. (Siegel)
- Preserve physician discretion in ordering, interpreting, and delivering diagnostics, therapies, and other forms of care. (Conti)
- Ensure that agency decision making is transparent, with rulemaking by notice and comment rather than through guidelines. (Conti)
- Standardize the validation of protocols and enhance quality control to improve the efficiency of test development. (van 't Veer)
- Provide guidance for IRBs on how to review genomic tests. (van 't Veer)
- Provide opportunities and incentives for guidelines committees and regulatory bodies to harmonize their definitions of clinical utility. (van 't Veer)
- Reform reimbursement to recognize the value of diagnostic tests, their impact on health care, and the resources needed to develop and validate tests. (Enns)
- Establish reliable and accurate performance standards for new genomic tests. (Enns)

of the possible and promising tests can be developed, so the system should enable more to be developed, not fewer.

With regard to the distinction between CLIA-regulated tests and FDA-approved tests, Shak said that "the devil is in the details." Either route could yield regulation that is fit for purpose. In that respect, looking at the purpose of a test and then deciding on the proper kind of regulation may be more appropriate than the opposite.

Leonard said that it may be inaccurate to contrast an FDA path with an LDT path because there are many different LDT paths. For example, the path is much different in academia than in industry. "Maybe we need to start talking about different LDT pathways and think about the benefits of each." van 't Veer agreed and also observed that the complexity of tests varies greatly. Some require many levels of analysis, data integration, and bioinformatics, while others are relatively simple molecular tests. In addi-

- Compare new genomic tests with traditional practices to establish comparative effectiveness. (Shak)
- Provide ways for patients to get their questions answered by health care providers at the point of clinical decision making. (Gorman)
- Begin test development by discussing the needs of patients rather than how to secure reimbursement for a procedure. (Gorman)
- Use a progressive or adaptive regulatory and reimbursement framework to reflect the accumulation of knowledge and reduction of uncertainty over time. (Tunis)
- Define evidentiary standards through a collaborative process involving regulators, payers, clinicians, patients, and other stakeholders. (Tunis)
- Clarify expectations about the clinical value of technologies to provide criteria for coverage. (Hochheiser)
- Develop standards to accelerate the deployment of genomic tests. (Hochheiser)
- Develop critical reasoning medicine to support coverage decisions even when data are incomplete. (Quinn)
- Develop a public health approach to genetics that evaluates the utility of genomic tests and their impacts at the population level. (Khoury)
- Create incentives for public or private funding of research beyond the discovery phase, for knowledge synthesis and stakeholder convening, and for public and provider education. (Khoury)
- Increase collaboration among and within agencies to enhance the efficiency of regulation. (Gutierrez)
- Create a standard nomenclature and taxonomy to enhance the efficiency of regulation. (Jacques)

tion, tests are used for different purposes, such as diagnosis versus treatment decisions, and regulation could be reflective of these differences.

An intermediate position proposed by Leonard is that FDA would formally decide what can go through an LDT pathway without FDA review based on risk-based stratification. This would be "a better strategy than eliminating the LDT pathway altogether," said Leonard, since there would be a negative impact on medical care if the LDT pathway did not exist. The LDT pathway can spur innovation, especially with tests used in low volumes, even if they pose difficulties with evidence generation.

Hayes stated that over the course of the day he had come to modify the proposal he set out at the beginning. Perhaps the LDT pathway should still exist, he said, but within FDA, so that a single review process with multiple pathways would exist. This would put more burden on FDA, but it would eliminate the need for many different assessment panels among third-party payers, because they could rely on FDA for review and approval, though

they still would have to set reimbursement levels. This system would be much more similar to how drugs are approved. "Genentech hasn't to my knowledge run around to every insurance company in the country and gotten approval for Herceptin," said Hayes. "It all happened because the FDA gave it approval." Instead, the money now spent by companies on technology assessment could be shifted to FDA to support the extra work needed for the agency to become the single arbiter of whether a diagnostic does or does not have clinical utility.

One problem, Jacques pointed out, is that the budget at least within CMS to do technology assessments is currently very limited. Another problem, Hochheiser observed, is that it is very difficult to arrive at the value of a test. Furthermore, tests have to have positive margins, not just value, to be commercially appealing.

CONSOLIDATING OFFICES WITHIN FDA

Workshop participants also discussed Hayes' idea of combining FDA offices into a single oncologic office that looks at both diagnostics and therapeutics. Leonard asked how that arrangement would help for diagnostic tests that do not have an accompanying drug. Also, she asked, would every major disease need its own office or standing committee?

Another point raised by Hayes is that reimbursements need to be commensurate with the amount of work needed to develop a diagnostic. Leonard asked how CMS and third-party payers can be convinced to pay more for a test than the cost of doing that test. Wylie Burke of the University of Washington, and chair of the Roundtable, observed that such evaluations would encompass not only clinical utility but cost-effectiveness, which is an interesting but radical proposal. Hayes responded that FDA could determine clinical utility while payers do analyses of cost-effectiveness.

Burke asked whether a process needs to be developed involving a broader set of stakeholders about evidence. (This issue is also addressed later in this chapter.) Hochheiser agreed that an effective structure needs to be established but that no such structure exists today, even though processes may exist.

Hayes pointed to ODAC as a structure that works. FDA does not have to take ODAC's advice but usually does. ODAC consists of clinicians, statisticians, patients, and other stakeholders and makes hard decisions, such as whether 3 months of extra survival on average is worthwhile. "There is process and structure to address it in a relatively rational and stakeholder [engaged] way," said Hayes.

Enns, however, said that he would not want to take a diagnostic test through ODAC and CDER. He is much more comfortable taking products through CDRH. ODAC does not know how diagnostic tests are developed

and how they work, he said. Hayes responded that ODAC could combine CDRH and CDER for oncologic products.

COLLABORATION BETWEEN FDA AND CMS

Another major theme of the discussions was the potential for FDA to work more closely with CMS so that decisions about regulatory approval and reimbursement are coordinated. The evidence requirements may not be the same, Leonard pointed out, but test developers would better understand the bars they have to surmount to get approval and then payment.

One problem, said Leonard, is that CMS covers procedures for older populations, but many procedures are aimed at other populations. Also, CMS has different concerns than private payers. Could a private payer group work with both FDA and CMS so that everyone is involved in the regulatory and reimbursement process? A possible incentive to do so is to make payments dependent on participation in such a process.

A conversation between FDA and CMS on reviewing the same evidence could, in some cases, lead to simultaneous regulatory approval and reimbursement, Tunis added. In other cases, it could lead to clarification of the divergence between the two agencies and what CMS is looking for in contrast to regulatory expectations. Parallel review could enable the agencies to clarify for themselves and for the outside world the difference between safe and effective and reasonable and necessary. However, Tunis did not expect greater cooperation to lead to harmonized or identical expectations about evidence because the regulatory expectations usually will be different. Instead, alignment will lead to greater predictability and clarity about how studies need to be designed to address the information needs of the regulators and what additional information is needed for reimbursement decisions and clinical decisions. However, Tunis also observed that it may not be scientifically or economically viable to demonstrate clinical utility for regulatory approval, much less reimbursement. Leonard suggested that NIH may increasingly be willing to consider funding for test validation research and that public-private partnerships also could consider funding evidence development for genomic tests to fill this gap.

Jacques said that once ongoing pilot studies are completed, parallel review will be more formalized and that only a few years should be needed to generate enough experience to develop a framework or guideline for collaboration. At the moment, offers by CMS to collaborate in a review generate "a polite yes, but a somewhat guarded yes. There is nothing that prevents [this] from happening now aside from the reluctance of sponsors to tell . . . FDA we would like you to invite CMS to our meetings," he said.

The bar for approval at CMS is higher than at FDA, which is one reason why the number of reviews FDA handles is much larger than at CMS,

Gutierrez stated. "Some people don't have the data or would not want to collect the data, at least at that time, for what it would require to have CMS's approval. They're not ready."

In response to a question about third-party reviews of LDTs, Gutierrez pointed out that FDA does have a third-party review process, though "it has never worked particularly well for diagnostics partly because the expertise hasn't existed." But pilot programs are in process, particularly involving third-party inspections done in other foreign countries. Also, the agency recognizes that more expertise is now available, especially for devices that are lower-risk, and some groups have expressed interest in doing third-party inspections. Jacques added that, while unable to discuss in detail, CMS is open to exploring some of these options.

CMS is exploring the potential to align coverage with evidence development with FDA's postmarket requirements. If FDA and CMS could agree with the sponsors of a particular protocol on a way to satisfy both CED and FDA requirements, that would be better than the current system. "In the current system, you have a postmarket requirement and no guarantee that there will be any Medicare funding going to support that," said Jacques. "It may take forever to accrue that study. If Medicare from day one is essentially saying we're going to go ahead and pay for the item or service in this particular context, it seems that you would be able to more efficiently address FDA's issues as well as our issues."

PROGRESSIVE APPROVAL AND REIMBURSEMENT PROCESSES

Collaboration among FDA, CMS, and private payers could facilitate coverage with evidence development or other progressive approval processes for regulation and reimbursement, Leonard said. However, this approach may only work for the LDT pathway given the regulatory and reimbursement systems that exist in the United States. Questions that would have to be answered are how to change the reimbursement level as data are generated, and how to get a test off the market if the evidence does not support its continued use.

van 't Veer said that a critical point is to get FDA and CMS to determine the common levels of evidence needed and common strategies of how to get something approved, while also circling back to the people who are developing the test, whether in industry or academia. Different types of tests need different levels of evidence, and these differences need to be integrated into work plans.

Payment decisions need standards that allow for further validation over time, said Leonard. Payers have their own groups that do assessments of evidence, so one question is how all payers could support a single decision.

Also, once a decision is made, how would compliance with that decision be ensured?

In various systems of progressive approval, observed Khoury, there would be continuous collection of information on clinical validity and utility where the stakeholders all agreed to the rules of engagement. As an example, he pointed to whole-genome sequencing. Existing evidence does not necessarily call for whole-genome sequencing, but if the sequence were available, the question could be asked, "What information is actionable in that whole-genome sequence under different clinical scenarios?" Such an approach would direct the conversation rather than forcing it to be reactive. "You can feed different processes that allow you to collect data, get the stakeholders together, fund the research, reimburse some of it, and have tighter controls at the outset."

Enns briefly mentioned models from other countries. For example, Japan does a simultaneous review of safety, effectiveness, and reimbursement coverage. The process in Japan takes far too long, said Enns, but perhaps it points toward a way for FDA and CMS to work together.

Burke also asked about partnerships that involve not just FDA and CMS but industry, providers, and patients. What are the barriers and incentives to partnering, she asked?

Innovative approaches other than CED also could yield valuable evidence, said Leonard. For example, the prospective-retrospective trial designs that Genomic Health used for Oncotype DX were an innovative design that worked. For prospective-retrospective designs, specimens from clinical trials need to be archived and clinical data need to be accessible, which adds to the cost of the designs. Also, clinical trial samples can be proprietary when they are sponsored by industry. NIH could make it a requirement that samples be archived and available when it funds a clinical trial, as is being done at the National Institute of Diabetes and Digestive and Kidney Diseases.

On the same topic, a participant said that one way to break the vicious cycle of undervalued genomic diagnostic tests is through coverage for field evaluation. That raises the question of when the evidence is strong enough to move to this type of evaluation process. Khoury agreed that such an arrangement is the only effective long-term way to develop genomic tests. "If you get stuck with either the highest level of evidence or nothing at all, genomics will never really come to light." Whole-genome analysis is an excellent example, because it is not currently useful except in looking for rare and undiagnosed genetic conditions, yet it contains plenty of actionable information.

Hayes pointed to some of the problems with progressive approval. Once a test is being widely used, it is much harder to evaluate, because people either believe that it should be used or should not be used, and a

true RCT is much more difficult. Instead, said Hayes, the level of evidence needed for clinical utility should be defined and money should be put into trials to achieve this level. "Let's get the trials done quickly by not allowing the assay to be available outside the trials, just like we do with drugs. Then we'll generate much higher levels of evidence much faster. In fact, the entrepreneurs will be rewarded for doing this because the reimbursement will be sufficient for them to do this, and the patients will be better off because we'll actually know how to use these things faster." In contrast, allowing an intermediate level of approval risks shutting down innovation "because it's already there and then it's harder to test."

Khoury said that RCTs may or may not be the answer and that information can also come from a variety of sources such as observational studies and modeling. The important thing is to design the rules ahead of time.

Another issue, said Hayes, is whether third-party payers should help fund the clinical trials. In some cases, they may want to be partners in evidence generation, but there has to be value for the third-party payer in the partnership, and partnerships should not be mandated.

Tunis also observed that making regulatory or coverage decisions with less evidence than has been the case in the past implies backloading the evidence requirements, which could increase innovation and economic development. "The only downside is putting the genie back in the bottle," Tunis said. "If things are going to get into the market earlier and more broadly with less evidence, then on the back end it's got to be easier to take things off the market. I don't know how to make that happen from a public acceptability point of view."

Hayes observed that new drugs cannot be on the market during a randomized trial of that drug. "The assumption is that the new drug must be worthwhile." Rather, new drugs undergo staged, conditional approvals based on settings. "Perhaps there are ways to do that with biomarkers."

However, Shak pointed out that the use of some drugs off label by physicians is allowed, which led him to the question of tracking what physicians actually do in practice. "What are the patterns we want to encourage, and what are the ones we want to discourage?" Quinn said that incentives should be in the right direction but that currently the systems to track what happens in practice are weak. Tunis observed that the sophisticated analysis of routinely collected data generated in the course of care could be informative about clinical utility, but the question needs to be asked whether such information will have sufficient reliability to inform decisions. "It goes back to my point . . . about defining evidentiary thresholds and strengths of evidence linked to certain kinds of decision making rather than just let's collect some information and hope that it happens to be informative. We've got to be more thoughtful about what the questions are, what the methods need to be, and then figure out how to do those studies, as opposed to we

happen to have access to this data from claims databases, electronic health records and let's not bother to do anything else."

Shak pointed to the example of the Cystic Fibrosis Foundation, which invested in a patient registry and is now feeding back quality metrics to individual centers. "They put that on the web so every family and patient with cystic fibrosis can see and compare their center to others. It really is a very innovative and creative way of empowering patients." At the same time, survival among cystic fibrosis patients has gone from 28 to 38 years in the past 10 to 15 years.

ARRIVING AT A COLLECTIVE SOCIAL JUDGMENT

More broadly, Burke asked how to arrive at what Tunis called a "collective social judgment" regarding the value of a genomic test. Different stakeholders can have different assessments of value. How can these differences be bridged, she asked?

Tunis observed that the process by which FDA derives regulatory guidance is one example of how to arrive at a collective social judgment, since it is an iterative public process in which there is a push and pull among stakeholders that occurs through a transparent process. Khoury also pointed to the experience with EGAPP, which was based on the model used by USPSTF for clinical preventive services. EGAPP developed methods and published evidence-based guidelines as well as recommendations and systematic reviews. It received pushback from some stakeholders, but Khoury said that the pushback amounted to shooting the messenger rather than the message. EGAPP is now modernizing its approaches to incorporate rapid evaluations and decision modeling so that it becomes more "nimble." One question is the extent to which stakeholders should be involved or the extent to which EGAPP should be independent.

Tunis also said that public–private partnerships could offer a forum for stakeholders to talk about a wide range of issues, including integrating payer and regulatory requirements and evidentiary thresholds. One example is the Foundation for the National Institutes of Health, which has been working on the validation of individual biomarkers. But even this consortium determined that setting evidentiary thresholds was beyond its scope. Partnerships may have value, but there may not be a marketplace demand or a business model to support such work. In that case, said Burke, perhaps its value to the full range of stakeholders needs to be articulated.

Leonard asked about the objectives of partnerships. Would they do evidence-based reviews for tests on the market, which are being done by AHRQ and other groups? Or would they decide whether tests are medically useful and whether they should be paid for or whether there should be

coverage with evidence development? Even if a group did that, who would pay attention to its recommendations?

Shak suggested that arriving at a collective social judgment may be a two-step process. In the first stage, there would be a dispassionate collection of evidence with transparency about what is known and what is not known. Phase two would then determine whether the benefits of a test outweigh the risks. It will not be possible to get 100 percent agreement on this second phase, he acknowledged. Rather, it will require having many perspectives at the table that can hash out differences and arrive at an assessment. He suggested that professional societies could serve in this role of convening advocates.

Hayes, however, observed that professional societies have perceived conflicts of interest and also that societies would be overwhelmed by the amount of work that needs to be done. Shak countered that the convening function could be structured to be open and transparent and avoid these conflicts. The societies could provide lead areas of expertise as medicine becomes more complicated.

Tunis agreed with the advantages of a two-step process but wondered who could bring together the many different stakeholders involved, from insurance companies to patient advocacy organizations to medical specialty societies. He also worried that such a process might sound like the creation of entities to determine effectiveness, value, availability, and price, which "sounds a whole lot like a rationing body."

Jacques pointed out that the inherent problem is trying to fund innovation using an insurance paradigm, which is inevitably reactive. An alternative model might be the one used by the Department of Defense, which specifies the performance characteristics of what is needed and determines how much it will spend to support the development of a product.

Khoury said that if the system were being reinvented, the most important component would be the convening of the stakeholder space. "You need the rules of engagement. You need a continuous process of knowledge synthesis so that you can inform the research enterprise. We need investors in that research enterprise. Then we need that space by which validated technology moves into practice in a way that makes sense." Billions of dollars are now being spent to make new discoveries. The additional expense of doing knowledge synthesis would not be that great, and without such a mechanism, the money spent on basic science discovery will not result in better health outcomes.

FINAL REMARKS

In his concluding remarks at the workshop, Robert McCormack of Veridex observed that the workshop uncovered an unprecedented amount

of information, some of which has never been uncovered before. In particular, he called attention to the importance of clarity. "The sheer confusion over the number of guideline groups that exist today, and the fact that they all don't have the same bar or standard, makes it very confusing for manufacturers. What makes it worse is that the playing field is always changing, and you don't know it's changing until it's already changed."

The legacy of the workshop is not what was said but will happen once it is over, said McCormack. "It's incumbent upon us now to identify those next steps . . . and to start putting into place some of those mechanisms to chip away and resolve some of these issues."

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Appendix A

Workshop Agenda

Facilitating Development and Utilization of Genome-Based Diagnostic Technologies: A Workshop

November 15, 2011

The Keck Center of the National Academies
500 Fifth Street, NW
Washington, DC 20001

WORKSHOP OBJECTIVE

To address the differences in evidence required for clinical use, regulatory oversight, and coverage for a laboratory test, as well as laboratory test reimbursement, with the goal of clarifying a pathway for successfully bringing a test to clinical use for the benefit of patients.

Focal Questions:

- What are your views of the described barriers to successful genomic test development?
- What are potential solutions?
- What are the obstacles to achieving those solutions?
- How can we overcome those obstacles?

8:30-8:35 A.M. **WELCOMING REMARKS**

Wylie Burke, *Roundtable Chair*
Professor and Chair, Department of Bioethics and Humanities, University of Washington

8:35-8:45 A.M. **CHARGE TO WORKSHOP SPEAKERS AND PARTICIPANTS**

Robert McCormack, *Workshop Co-Chair*
Head of Technology Innovation and Strategy, Veridex, LLC

8:45-9:15 A.M. **REVIEW OF NOVEMBER 2010 WORKSHOP "GENERATING EVIDENCE FOR GENOMIC DIAGNOSTIC TEST DEVELOPMENT" AND STATEMENT OF PROBLEM**

Debra Leonard, *Workshop Co-Chair*
Professor and Vice Chair, Department of Pathology and Laboratory Medicine; Director of the Clinical Laboratories, Weill Cornell Medical Center

9:15-10:15 A.M. **ADVANCING UTILITY AND ADOPTION OF CLINICAL GENOMIC DIAGNOSTICS—PART I**

Moderator: Robert McCormack, Veridex, LLC

Daniel Hayes
Clinical Director of the Breast Oncology Program and Stuart B. Padnos Professor in Breast Cancer Research, University of Michigan Comprehensive Cancer Center

Muin Khoury
Director, National Office of Public Health Genomics, Centers for Disease Control and Prevention

	Laura van 't Veer Angela and Shu Kai Chan Endowed Chair in Cancer Research; Leader, Breast Oncology Program; Director, Applied Genomics, UCSF Helen Diller Family Comprehensive Cancer Center
	Russel K. Enns Chief Regulatory Officer, Cepheid
10:15-10:45 A.M.	Discussion with Speakers and Attendees
10:45-11:00 A.M.	BREAK
11:00 A.M.-12:00 P.M.	**ADVANCING UTILITY AND ADOPTION OF CLINICAL GENOMIC DIAGNOSTICS—PART II**
	Moderator: Debra Leonard, Weill Cornell Medical Center
	Steven Shak Chief Medical Officer, Genomic Health, Inc.
	Mark Gorman Director of Survivorship Policy, National Coalition for Cancer Survivorship
	Nicholas Conti Vice President, Business Development, Quest Diagnostics
	Sue Siegel General Partner, Mohr Davidow
12:00-12:30 P.M.	Discussion with Speakers and Attendees
12:30-1:15 P.M.	WORKING LUNCH

1:15-2:00 P.M.	**ADVANCING UTILITY AND ADOPTION OF CLINICAL GENOMIC DIAGNOSTICS—PART III**
	Moderator: Robert McCormack, Veridex, LLC
	Bruce Quinn Senior Health Policy Specialist, Foley Hoag LLP
	Sean Tunis Director, Center for Medical Technology Policy
	Louis Hochheiser Medical Director Clinical Policy, Humana, Inc.
2:00-2:30 P.M.	Discussion with Speakers and Attendees
2:30-3:20 P.M.	**EVALUATING PATHS FORWARD FOR ADVANCING MOLECULAR DIAGNOSTICS THROUGH REGULATORY AND REIMBURSEMENT POLICY**
	Moderator: Debra Leonard, Weill Cornell Medical Center
	Alberto Gutierrez Director, Office of In Vitro Diagnostic Device Evaluation and Safety, Center for Devices and Radiological Health, U.S. Food and Drug Administration
	Louis Jacques Director, Coverage and Analysis Group, Office of Clinical Standards and Quality, Centers for Medicare & Medicaid Services
3:20-3:30 P.M.	BREAK
3:30-4:15 P.M.	Discussion with Speakers and Attendees

4:15-5:30 P.M.	FACILITATING CONVERGENCE
	Moderator: Wylie Burke, University of Washington
	Panel Discussion with Prior Speakers
5:30-5:45 P.M.	**Concluding Remarks**
	Robert McCormack, *Workshop Co-Chair* Head of Technology Innovation and Strategy, Veridex, LLC
	Debra Leonard, *Workshop Co-Chair* Professor and Vice Chair, Department of Pathology and Laboratory Medicine; Director of the Clinical Laboratories; Weill Cornell Medical Center
6:00 P.M.	**ADJOURN**

Appendix B

Speaker Biographical Sketches

Wylie Burke, M.D., Ph.D., is professor and chair of the Department of Bioethics and Humanities at the University of Washington. She received a Ph.D. in genetics and an M.D. from the University of Washington and completed a residency in internal medicine at the University of Washington. She was a Medical Genetics Fellow at the University of Washington from 1981 to 1982. Dr. Burke was a member of the Department of Medicine at the University of Washington from 1983 to 2000, where she served as Associate Director of the Internal Medicine Residency Program and founding Director of the University of Washington's Women's Health Care Center. She was appointed Chair of the Department of Medical History (now the Department of Bioethics and Humanities) in October 2000. She is also an adjunct professor of medicine and epidemiology and a member of the Fred Hutchinson Cancer Research Center. She is a member of the Institute of Medicine and the Association of American Physicians, and is a past President of the American Society of Human Genetics. Dr. Burke's research addresses the social, ethical, and policy implications of genetics, including responsible conduct of genetic and genomic research, genetic test evaluation, and implications of genomic health care for underserved populations. She is director of the University of Washington Center for Genomics and Healthcare Equality, a National Human Genome Research Institute Center of Excellence in Ethical, Legal, and Social Implications research, and co-director of the Northwest-Alaska Pharmacogenomic Research Network.

Nicholas Conti, Ph.D., M.B.A., is Vice President, Business Development for Quest Diagnostics. He is responsible for licensing and technology transac-

tions as well as the development and management of strategic alliances for the company. He has led licensing efforts which have resulted in licensing dozens of new technologies that have been developed into new clinical assays. Dr. Conti joined Quest Diagnostics in 2006. Prior to joining the company, he was Vice President, Business Development, for Becton Dickinson. Dr. Conti started his career at Union Carbide as a scientist engaged in catalysis research for their plastics division. Dr. Conti is a graduate of Notre Dame with a bachelor's degree in chemistry. He received his Ph.D. in chemistry from the University of Florida and his M.B.A. from the Wharton School. Additionally, Dr. Conti is an Overseas Fellow of the Royal Society of Medicine.

Russel K. Enns, Ph.D., is the Chief Regulatory Officer of Cepheid overseeing staff and departments in Regulatory, Clinical and Government Affairs and Quality Systems and Compliance. He has been at Cepheid since June 2003. From 2001 to 2003 he was Divisional Vice President of Regulatory and Clinical Affairs, Quality Systems and Medical Reimbursement at Vysis (wholly owned by Abbott Laboratories), a genomic disease management company. Prior to the Abbott acquisition he served the same functions as above since 1995. Before joining Vysis, he was Vice President, Technical Affairs of MicroProbe Corporation, from 1992 to 1995. MicroProbe was sold to Becton Dickinson in 1995. Before joining MicroProbe, he held various positions at Gen-Probe, Inc. (a biotechnology diagnostic company), in order of Director of Product Development, Clinical Programs, and Technical Affairs from 1984 to 1992. Dr. Enns was the Director of Cell Biology R&D at Alpha Therapeutics Corporation from 1979 to 1984. From 1975 to 1979 he was a Senior Research Biochemist at Monsanto Corporation. He received his Ph.D. in biochemistry from the University of California, Davis, in 1976. He was a national foundation lecturer for ASM from 1988 to 1989. From 2005 to 2011 he served on the Clinical and Laboratory Standards Institute Board of Directors, and he was a co-founder and chair of its Area Committee on Molecular Methods from 1992 and 1998 to 2005, respectively. Dr. Enns has helped introduce approximately 35 different molecular diagnostic products and platforms through the in vitro diagnostic process at the Food and Drug Administration (FDA) since 1985, including infectious disease, oncology, and genetic tests.

Mark Gorman is Director of Survivorship Policy for the National Coalition for Cancer Survivorship (NCCS). He is a long-term survivor of metastatic melanoma. His work with NCCS focuses on advocacy for quality cancer care for all people touched by cancer. NCCS looks to the six aims of quality identified in *Crossing the Quality Chasm* for a framework for its advocacy. He has served on the EGAPP Stakeholders Group, the External Stakehold-

ers Advisory Group for the CANCERGEN project, and as consumer faculty for the Accelerating Anti-Cancer Agent Development and Validation Workshop. He is also an FDA Patient Consultant for Melanoma.

Alberto Gutierrez, Ph.D., is the Director of FDA's Office of In Vitro Diagnostic Device Evaluation and Safety. Dr. Gutierrez received a bachelor's degree from Haverford College, and master and doctorate degrees in chemistry from Princeton University. Dr. Gutierrez has over 10 years of experience in research in the area of structural organic and organometallic chemistry. Dr. Gutierrez joined FDA in 1992 as researcher and reviewer in FDA's Center for Biologics Evaluation and Research working on vaccine adjuvants and method development for determination of purity and structure of vaccine components. In 2000, he joined the Office of In Vitro Diagnostic Device Evaluation and Safety as a scientific reviewer, becoming a Team leader for Toxicology in 2003, Director of the Division of Chemistry and Toxicology Devices in 2005, Deputy Director of the Office of In Vitro Diagnostic Devices in 2007, and Director in 2009.

Daniel F. Hayes, M.D., is the Clinical Director of the Breast Oncology Program at the University of Michigan Comprehensive Cancer Center (UM CCC), where he is the Stuart B. Padnos Professor of Breast Cancer Research. He received a bachelor's degree (1974) and a master's degree (1977) at Indiana University. He received his M.D. from the Indiana University School of Medicine in 1979, followed by a residency in internal medicine at the University of Texas Health Science Center at Dallas, Texas (hence renamed University of Texas Southwestern Medical Center at Dallas; Parkland Memorial and affiliated hospitals). He served a fellowship in medical oncology from 1982 to 1985 at Harvard's Dana Farber Cancer Institute (DFCI) in Boston. In 1992, he assumed the role of the Medical Director of the Breast Evaluation Center at DFCI. He held that title until 1996, when he moved to the Georgetown University Lombardi Cancer Center. In 2001, Dr. Hayes joined the UM CCC and continues treating patients and doing research in translational science. Dr. Hayes and colleagues published the first reports concerning the development of the CA15-3 blood test, which is currently used worldwide to evaluate patients with breast cancer. He has become an internationally recognized leader in the use of this and other tumor markers, such as HER-2, circulating tumor cells, and pharmacogenomics. In 2007, he was awarded the American Society of Clinical Oncology's (ASCO) Gianni Bonadonna Breast Cancer Award. He is Chair of the Breast Cancer Translational Medicine Committee of the Southwest Oncology Group (SWOG), Chair of the Correlative Sciences Committee of the U.S. Breast Cancer Intergroup, and co-chairs the Expert Panel for

Tumor Marker Practice Guidelines for ASCO. In 2011, he was elected to the ASCO Board of Directors (2011-2014).

Louis Hochheiser, M.D., is Medical Director for Clinical Policy Development in the Clinical Guidance Organization for Humana, Inc., in Louisville, Kentucky. In this position, he provides leadership for the technology assessment process, policy implementation, strategy for molecular diagnostics, and oversight for medical director reviews. He earned his B.A. (1958) from the University of Pennsylvania in Philadelphia, and his M.D. in 1962 from the New Jersey Medical College in Newark, New Jersey. He conducted his rotating internship at the U.S. Naval Hospital in St. Albany, New York; completed his residency in pediatrics at Kaiser Hospital in San Francisco, California; and did a fellowship in community pediatrics at the University of Rochester in New York. Additionally, he served as a Lieutenant in the U.S. Navy. His background includes 17 years as Chairperson of Family Medicine, first at Brown University and then the University of Vermont, where he holds the position of professor emeritus. He has published abstracts, journal articles, and book chapters, as well as lectured extensively on the topics of pediatric health, quality of care, nurse practitioner education, and family dynamics. He is also professor emeritus at the University of Vermont and the Medical Director Clinical Policy Development for Humana, Inc., in Jackson, Wyoming.

Louis B. Jacques, M.D., joined the Centers for Medicare & Medicaid Services (CMS) in 2003 and has been director of the Coverage and Analysis Group (CAG) since October 2009. The group reviews evidence and develops Medicare national coverage policies. From 2004 through 2009 he was Director of the Division of Items and Devices within CAG. Prior to his arrival at CMS, Dr. Jacques was the Associate Dean for Curriculum at Georgetown University School of Medicine, where he retains a faculty appointment. He served on a number of university committees including the Executive Faculty, Committee on Admissions, and the Institutional Review Board. He previously worked in the Palliative Care program at Georgetown's Lombardi Cancer Center, where he covered the gynecologic oncology service and he made home visits as a volunteer physician for a rural hospice on the Maryland Eastern Shore.

Muin Khoury, M.D., Ph.D., is the first Director of the Centers for Disease Control and Prevention's (CDC's) National Office of Public Health Genomics. The Office was formed in 1997 to assess the impact of advances in human genetics and the Human Genome Project on public health and disease prevention. CDC's National Office of Public Health Genomics serves as the national focus for integrating genomics into public health research

and programs for disease prevention and health promotion. Dr. Khoury joined CDC as an Epidemic Intelligence Service Officer in 1980 in the Birth Defects and Genetic Diseases Branch, and as a medical epidemiologist in 1987. In 1990, he became Deputy Chief of the same branch. In 1996, Dr. Khoury chaired a CDC-wide Task Force on Genetics and Disease Prevention and provided important leadership in outlining a plan delineating the future direction that CDC should take in this important area. Dr. Khoury received his B.S. degree in biology and chemistry from the American University of Beirut, Lebanon, and his medical degree and pediatrics training from the same institution. He received a Ph.D. in human genetics and genetic epidemiology and training in medical genetics from Johns Hopkins University. Dr. Khoury is board certified in medical genetics. Dr. Khoury has published extensively in the fields of genetic epidemiology and public health genetics and is a member of many professional societies and serves on the editorial boards of several journals. He is an adjunct professor of epidemiology at Emory's School of Public Health and an associate in the Department of Epidemiology at Johns Hopkins University Bloomberg School of Public Health.

Debra Leonard, M.D., Ph.D., received her M.D. and Ph.D. from the New York University School of Medicine, and is currently Professor and Vice Chair for Laboratory Medicine in the Department of Pathology and Laboratory Medicine, and Director of the Clinical Laboratories for New York-Presbyterian Hospital's Cornell campus (NYPH-WCMC). She is also Director of the Pathology Residency Training Program at NYPH-WCMC. Dr. Leonard was previously Director of Molecular Pathology at the University of Pennsylvania School of Medicine and is a nationally recognized expert in Molecular Pathology. She has served on several national committees that develop policy for the use of genetic and genomic technologies and information, including most recently the Secretary's Advisory Committee on Genetics, Health and Society that advises the Secretary of Health and Human Services. Dr. Leonard is editor of two molecular pathology textbooks and has spoken widely on various molecular pathology test services, the future of molecular pathology, and the impact of gene patents on molecular pathology practice. Dr. Leonard is interested in the use of genomic technologies in the practice of medicine to improve patient outcomes.

Robert McCormack, Ph.D., is currently Head of Technology Innovation and Strategy for Veridex, LLC. He was formerly the Director of Technology Assessment of Ortho-Clinical Diagnostics, which focused on novel cellular and molecular cancer technology. In 2005 he assumed the role of Vice President of Scientific and Medical Affairs at Veridex, LLC, a Johnson & Johnson startup dedicated to the development and commercialization of novel cancer diagnostic tests. His group successfully conducted clinical

trials to launch the first molecular test for assessing axillary nodal status in women diagnosed with breast cancer. Prior to this position, in 2001 he was appointed General Manager of the Cellular Diagnostics Group at Veridex. The Cellular Diagnostics Group successfully launched their first product in 2004 for the detection and enumeration of circulating tumor cells in patients with metastatic breast cancer. He joined Johnson & Johnson in 1998 as Vice President of Clinical Affairs for Ortho-Clinical Diagnostics. Under his direction, Ortho-Clinical Diagnostics became the first diagnostics company to gain FDA approval for hepatitis assay testing on random access automation for clinical laboratories. In 1995 he joined Sanofi Diagnostics Pasteur as Director of Clinical and Regulatory Affairs, and Worldwide Group Leader for cancer diagnostics. Dr. McCormack spent his early career in genetic, molecular, and cellular research at the University of Minnesota, 3M, and Hybritech. He transitioned to clinical and regulatory affairs at Hybritech and was part of the team that successfully gained FDA approval for prostate-specific antigen (PSA) in the early detection of prostate cancer. Dr. McCormack received his B.S. degree in medical technology from the University of Wisconsin, River Falls, and his M.S. and Ph.D. degrees from the University of Minnesota in hematology and immunology, respectively.

Bruce Quinn, M.D., Ph.D., is a national expert on Medicare policy, the impact of health reform on innovation, and the crafting of successful business strategies within the U.S. health care reimbursement system. Dr. Quinn has worked successfully with both large and small companies in overcoming hurdles to commercialization through negotiation, understanding insightful ways to use the existing system to advantage, and the mechanisms of policy change. Since 2008, Dr. Quinn has been a full-time business strategist working with attorney and policy teams for health care and life sciences clients in the firm's Government Strategies practice. Dr. Quinn travels nationwide to speak on health reform issues and publishes actively, recently writing two peer-reviewed policy articles on advanced diagnostics. Before joining Foley Hoag LLP, he was the regional Medicare medical director for the California Part B program. Earlier in his career, Dr. Quinn was a physician executive in the Health & Life Sciences division of Accenture, working with the pharma, biotech, and genomics industries. Dr. Quinn is a board-certified pathologist. As a physician-scientist on the faculty of Northwestern University School of Medicine, he led pathology research for Northwestern's National Institutes of Health–funded Alzheimer Research Center. Earlier, he also held academic positions at New York University School of Medicine and the UCLA Center for Health Sciences and is the author or co-author on 30 scientific publications, including two 2010 publications on personalized medicine policy. He also holds an MBA from the Kellogg School of Northwestern University.

Steven Shak, M.D., has served as Chief Medical Officer with Genomic Health, Inc., since 2000. Under Dr. Shak's leadership Genomic Health used innovative molecular diagnostic methods and rigorous clinical studies to develop the Onco*type* DX® breast cancer and colon cancer assays and has maintained an 80 percent product development success rate. Dr. Shak has been a leader in personalized medicine for more than two decades. Prior to co-founding Genomic Health in 2000, he served for 14 years in various roles in Discovery Research and Medical Affairs at Genentech, Inc., a biotechnology company dedicated to using human genetic information to discover, develop, manufacture, and commercialize medicines to treat patients with serious or life-threatening medical conditions. He led the clinical team that gained approval for Herceptin®, a targeted biologic treatment for breast cancer. He also initiated the cancer clinical trials of the anti-angiogenesis agent Avastin®. In addition, Dr. Shak discovered Pulmozyme®, a mucus-dissolving enzyme that is approved worldwide for the treatment of the genetic disease cystic fibrosis. Prior to joining Genentech, he was an assistant professor of medicine and pharmacology at New York University School of Medicine. Dr. Shak holds a bachelor of arts degree in chemistry from Amherst College and an M.D. from New York University School of Medicine, and completed his postdoctoral training at the University of California, San Francisco.

Susan E. Siegel, M.S., is a General Partner at Mohr, Davidow, a leading Silicon Valley venture firm. Ms. Siegel leads investments in companies involved in personalized medicine, digital health, and life sciences, tools, and molecular diagnostics. Prior to her venture capital career, Ms. Siegel spent more than 20 years as a corporate leader growing biomedical companies through the commercialization of breakthrough technologies, including Bio-Rad, DuPont, Amersham (now GE), and Affymetrix. As President and Director of Affymetrix, Inc., Ms. Siegel focused on customer engagement and building shareholder value, leading Affymetrix growth to a multibillion-dollar market cap company. As a leading genomic company, Affymetrix accelerated the advent of personalized medicine. Ms. Siegel serves as a board member for Pacific Biosciences, Crescendo Bioscience, Corventis, Navigenics, On-Q-ity, Newtco, Analyte Health, Personalis, and RainDance Technologies. She also serves on DELL's Healthcare and Life Sciences Advisory Board. In addition, Ms. Siegel is a member of the Presidents' Circle of the National Academies, sits on the Stanford Medical School's ITI Council, and is a member of the Santa Clara University Center for Science, Technology, and Society Board. Ms. Siegel was elected as a Henry Crown Fellow of the Aspen Institute, is a member of the Young Presidents Organization and of Women Corporate Directors. Ms. Siegel co-founded with Stanford Hospital, *Checking-In*™, an organization dedicated to serving the local

aging population. She is Board Member Emeritus of the Silicon Valley Tech Museum and of the Gladstone Advisory Council.

Sean R. Tunis, M.D., M.Sc., is the Founder and Director of the Center for Medical Technology Policy (CMTP) in Baltimore, Maryland. CMTP's main objective is to improve the quality, relevance, and efficiency of clinical research by providing a neutral forum for collaboration among experts, stakeholders, and decision makers. Dr. Tunis was a member of the Institute of Medicine Committee on Initial National Priorities for Comparative Effectiveness Research. He advises a wide range of domestic and international public and private health care organizations on issues of comparative effectiveness, evidence-based medicine, clinical research, reimbursement, and health technology policy. Through September 2005, Dr. Tunis was the Chief Medical Officer at CMS, where he had lead responsibility for clinical policy for the Medicare and Medicaid programs. Previously he served as the Director of the Health Program at the Congressional Office of Technology Assessment and as a health policy advisor to the U.S. Senate, where he worked on pharmaceutical and device policy issues. Dr. Tunis trained at UCLA and at the University of Maryland in internal medicine and emergency medicine, and holds adjunct faculty positions at the Center for Health Policy at Stanford University, the Department of Internal Medicine at the Johns Hopkins School of Medicine, and the Department of Surgery at the University of California, San Francisco.

Laura J. van 't Veer, Ph.D., is a professor of laboratory medicine, Leader of the Breast Oncology Program, and Director of Applied Genomics with the University of California, San Francisco Department of Pathology and Laboratory Medicine. She specializes in Breast Cancer and Applied Genomics. Dr. van 't Veer cofounded Agendia B.V. in 2003 and serves as its Chief Research Officer. She served as Chief Operating Officer of Agendia B.V. until June 12, 2007. Dr. van 't Veer served as the Head of the DNA-diagnostic laboratory of the Netherlands Cancer Institute (NKI) and also serves as a staff member of the Department of Molecular Pathology. She has 20 years of experience in molecular oncology research. She served as the Head of the Family Cancer Clinic of NKI for 10 years. She developed Agendia's MammaPrint® gene expression profiling service. She served as a Member of Group Counsel of Batenburg Beheer NV. She serves as a Director of the American Association for Cancer Research. She has published more than 80 papers in peer-reviewed journals.

Appendix C

Statement of Task

An ad hoc planning committee will plan and conduct a public workshop that will examine methods for accelerating the approval and adoption of genomic diagnostic tests. The workshop will feature presentations and discussions from an array of stakeholders which may include providers, payers, guideline developers, diagnostic device developers, product reviewers, patients, and regulators. The goal of the workshop will be to advance discussions among policymakers and the broader public on the current challenges which are limiting the development and utilization of diagnostic tests, such as commercial considerations, regulatory policy, and evidence of clinical utility. The planning committee will develop the workshop agenda, select and invite speakers and discussants, and moderate the discussions. An individually-authored summary of the workshop will be prepared by a designated rapporteur in accordance with institutional policy and procedures.

Appendix D

Registered Attendees

Reza Alavi
Center for Medical Technology Policy

William Albuquerque
Genetic Alliance

C. Anthony Altar
AssureRx Health, Inc.

Eric Assaraf
Washington Research Group

David Bachinsky
Alpha-Genics

Judith Benkendorf
American College of Medical Genetics and Genomics

Sharon Bergquist
National Academy of Sciences

Paul Billings
Life Technologies

Bruce Blumberg
Kaiser Permanente

Juli Bollinger
Genetics and Public Policy Center

Denise Bonds
National Heart, Lung, and Blood Institute

Khaled Bouri
U.S. Food and Drug Administration

Chandra Branham
AdvaMed

Joel Brill
Predictive Health, LLC

Steven Brotman
AdvaMed

Jonca Bull
Novartis

Wylie Burke
University of Washington

Khatereh Calleja
AdvaMed

C. Thomas Caskey
Baylor College of Medicine

Niranjana Chandrasekaran
Genetic Alliance

John Cogswell
Bristol-Myers Squibb

Nicholas Conti
Quest Diagnostics

Sara Copeland
Health Resources and Services Administration

Amy Cunniffe
Caris Life Sciences

Bernard Edelman
Vietnam Veterans of America

Russel Enns
Cepheid

W. Gregory Feero
National Human Genome Research Institute

Andrew Freedman
National Cancer Institute

Geoffrey Ginsburg
Duke University

Jonathan Gitlin
National Human Genome Research Institute

Judith Glassgold
Office of Rep. Sander Levin

Joseph Glick
Expertool Software

Federico Goodsaid
Vertex Pharmaceuticals

Mark Gorman
National Coalition for Cancer Survivorship

Johanna Gray
CRD Associates

David Gross
College of American Pathologists

Alberto Gutierrez
U.S. Food and Drug Administration

Chris Havasy
Presidential Commission for the Study of Bioethical Issues

Daniel Hayes
University of Michigan Comprehensive Cancer Center

C. J. Hoban
Multiple Myeloma Research Foundation

Louis Hochheiser
Humana, Inc.

Richard Hodes
National Institute on Aging

Gillian Hooker
National Human Genome Research Institute

Louis Jacques
Centers for Medicare & Medicaid Services

Janet Jenkins-Showalter
Roche/Genentech

Michael Evan Johnson
SWIDE Effects LLC

Sharon Kardia
University of Michigan

James Kelly
Affymetrix

Mohamed Khan
Vancouver Cancer Centre

Christopher Khoury
PwC

Muin Khoury
Centers for Disease Control and Prevention

Vanessa King
Siemens Corporate Research

Brenda Kostelecky
National Cancer Institute

Jennifer Leib
HealthFutures, LLC

Emily Lenneville
Institute of Medicine

Debra Leonard
Weill Cornell Medical Center

Hallie Lewis
Cepheid

Rachel Lindor
Department of Health and Human Services

Kimberly Linthicum
Myriad Genetic Laboratories

Paul Lipkin
Kennedy Krieger Institute

Michele Lloyd-Puryear
Office of Rare Diseases Research, National Institutes of Health

Jenny Luray
BD

Anthony Magliocco
H. Lee Moffitt Cancer Center

Debra Mathews
Presidential Commission for the Study of Bioethical Issues

Robert McCormack
Veridex, LLC

Mary McGrane
U.S. Department of Agriculture

Kasinathan Muralidharan
Quest Diagnostics Nichols Institute

Rachel Novak
U.S. Food and Drug Administration

Robert Nussbaum
University of California, San Francisco, School of Medicine

Steve Olson
Independent Consultant

Danielle Pambianco
HillCo HEALTH

Meeta Patnaik
Transtek Clinical Systems

Mary Pendergast
Pendergast Consulting

Michelle Penny
Eli Lilly and Company

Margaret Piper
Blue Cross and Blue Shield Association

Laura Povlich
American Association for the Advancement of Science Congressional Fellow—Office of Rep. Sander Levin

Aidan Power
Pfizer Inc.

Bruce Quinn
Foley Hoag LLP

Scott Rabuka
DNA Genotek

Turna Ray
GenomeWeb

Michael Reiner
Siemens Healthcare

Stephen Richardson
Genomic Health, Inc.

Allen Roses
Duke University

Tharini Sathiamoorthy
AdvaMedDx

Manon Schladen
Medstar Health Research Institute

Kevin Schulman
Duke University Medical Center

Joan Scott
National Coalition for Health Professional Education in Genetics

Beverlyn Settles-Reaves
Howard University

Steven Shak
Genomic Health, Inc.

Fay Shamanski
College of American Pathologists

Marilee Shelton-Davenport
National Research Council

Sophie Shen
The Brookings Institution

Vaidehi Sheth
Genetic Alliance

Andy Shih
Autism Speaks

Sue Siegel
Mohr Davidow

Jennifer Skornik
Independent

Dennis Strickland
Pfizer Inc.

Katherine Johansen Taber
American Medical Association

Wendy Toler
Medscientia

Sean Tunis
Center for Medical Technology Policy

Martha Turner
American Nurses Association

Laura van 't Veer
University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center

Michael S. Watson
American College of Medical Genetics and Genomics

Jennifer Webster
Kaiser Permanente Center for Heath Research

Susan Weiner
Children's Cause for Cancer Advocacy

Cole Werble
The RPM Report

Catherine Wicklund
Northwestern University

Yining Xie
National Institutes of Health

Huichun Xu
National Institutes of Health

Jiwen Zhang
GE Healthcare