Refining Processes for the Co-Development of Genome-Based Therapeutics and Companion Diagnostic Tests: Workshop Summary

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REFINING PROCESSES FOR THE CO-DEVELOPMENT OF GENOME-BASED THERAPEUTICS AND COMPANION DIAGNOSTIC TESTS

WORKSHOP SUMMARY

Sarah H. Beachy, Samuel G. Johnson, 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."
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The Roundtable wishes to express its gratitude to the expert speakers whose presentations helped outline the challenges in as well as the opportunities to co-developing genomic-based therapeutics and companion diag-

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Abbreviations and Acronyms

ACLA	American Clinical Laboratory Association
ACO	accountable care organization
AdvaMed	Advanced Medical Technology Association
ASCO	American Society of Clinical Oncology
CAP	College of American Pathologists
CISH	chromogenic in situ hybridization
CLIA	Clinical Laboratory Improvement Amendments
CMS	Centers for Medicare & Medicaid Services
EGFR	epidermal growth factor receptor
EQA	external quality assurance
FDA	U.S. Food and Drug Administration
FISH	fluorescence in situ hybridization
HER2	human epidermal growth factor receptor 2
IHC	immunohistochemistry
IOM	Institute of Medicine
IVD	in vitro diagnostic
LDT	laboratory-developed test

NGS	next-generation sequencing
NSCLC	non-small-cell lung cancer
PCR	polymerase chain reaction
RCT	randomized controlled trial

1

Introduction[1]

The initial fruits of the human genome project are beginning to be seen, with novel technologies based on genomic information being implemented in clinical practice. At the same time, however, the cost of developing new technologies has risen at a significant rate. With new pharmaceuticals estimated to cost more than $1 billion on average to develop and to take 10 years to bring to market (DiMasi et al., 2003), many drug developers have examined new strategies for creating efficiencies in their development processes, including the adoption of genomics-based approaches.

Genomic data can identify new drug targets for both common and rare diseases, can predict which patients are likely to respond to a specific treatment, and has the potential to significantly reduce the cost of clinical trials by reducing the number of patients that must be enrolled in order to demonstrate safety and efficacy. Somatic genome information can be used to guide therapy for cancer treatment and germline information can be used to assess risk of inherited diseases and to avoid adverse reactions to drugs. Recently, the expectation of such benefits has led to the development and approval of a number of targeted therapeutics for diseases such as non-small-cell lung cancer, metastatic melanoma, and cystic fibrosis (Chiang and Million, 2011; Davis et al., 2012). A key component of each of these new

[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.

drug approvals is the ability to identify the population of patients who will benefit from treatment, and this has largely hinged on the co-development and co-submission to the U.S. Food and Drug Administration (FDA) of a companion diagnostic test. The co-development process, or the development of the test and drug for the simultaneous submission to FDA,[2] has led to a major alteration in the way that drugs are being developed, with traditionally separate entities—pharmaceutical and diagnostic companies—now working in close collaboration.

While these early co-development successes have bolstered the industry and demonstrated to some extent the efficacy of a genomics-based approach to drug discovery and development, this convergence has not occurred without issue (Moore et al., 2012). Questions remain regarding the regulatory pathway (see Box 1-1) and reimbursement, the economic model, and clinical lab challenges. There is concern over the regulatory uncertainty that exists for companion diagnostic tests in particular over whether they should either be reviewed by FDA or through oversight by the Clinical Laboratory Improvement Amendments of 1988 (CLIA) or by a risk-based triage approach by FDA to determine which pathway should be used (Chapter 6). Payment is also a concern for laboratory-developed tests (LDTs) and in vitro diagnostics (IVDs) as well as follow-on tests (Chapters 5 and 6). Economic considerations concerning the co-development of companion diagnostic tests include the low reimbursement compared to value, the competition with LDTs that can erode IVD developer investments,[3] and the process by which drug and test companies partner for co-development (Chapters 4 and 6). From the clinical lab perspective, the result from a companion diagnostic test provides just one piece of information about the complexity of the disease, which makes assessing clinical utility for decision making a challenge. Technical problems also exist, including limited sample quantities available for testing (Chapter 3). There is also interest from stakeholders about how next-generation sequencing (NGS) will affect the regulation and use of companion diagnostics, especially after the approval of a test (Chapters 2–3 and 5–6).

[2]For the purposes of this workshop summary, an in vitro diagnostic (IVD), as defined by FDA, is considered a device, and is used to make a diagnosis of disease or other condition. It can also be useful for determining how to treat or prevent disease. A laboratory-developed test (LDT) is not FDA-approved and is developed and used by an individual laboratory. An FDA-approved companion diagnostic is an IVD that is used as a tool to provide additional decision-informing information about the safety and likely effectiveness of a related therapy. IVDs and LDTs are regulated differently (see Box 1-1).

[3]Recent U.S. Supreme Court Decisions on patentable material could have the potential for lasting impacts on co-development. It will take time to fully realize the economic and developmental implications of the rulings. See: *Association for Molecular Pathology v. Myriad Genetics*, 569 U.S. 12-398 (2013) and *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 10-1150 (2012).

BOX 1-1
Overview of Companion Diagnostic Test Regulation

FDA defines a companion diagnostic test as a device that "provides information that is essential for the safe and effective use of a corresponding therapeutic product" by identifying those patients who are most likely to benefit from treatment or who are at an increased risk of an adverse reaction or by providing information used in adjusting treatment (FDA, 2011). To further clarify the co-development review process, in July 2011, FDA issued draft guidance on co-development for developers of IVD tests and therapeutics (FDA, 2011). FDA's companion diagnostics process was designed to accommodate the co-development of a drug with a companion diagnostic test for identification of the subpopulation of patients most likely to respond to the drug. According to the guidance, IVDs developed as companion diagnostics for targeted therapeutics are subject to approval by FDA. The FDA framework for the risk-based regulation of devices involves assigning them to one of three classes, from those devices that have a low likelihood of harm (Class I) to those with high or unknown risk of harm (Class III). An FDA-approved companion diagnostic test is an IVD and is considered by FDA for use in aiding in the diagnosis of disease or another condition and can provide information about disease treatment and prevention. Because companion diagnostics direct treatment decisions, FDA has generally viewed them as high-risk Class III devices that require premarket approvals.

While FDA assesses the analytical and clinical validity of IVDs in its review process, it does not formally assess their clinical utility. However, in the case of companion diagnostic tests, clinical utility may be demonstrated during the course of the Phase III clinical trial for the drug. During this stage, the experimental drug is compared with the current therapy standard and additional information is collected on the effectiveness, side effects, and safety of the given therapy so that FDA can determine whether it will be approved for sale.

After FDA issued its draft guidance, many questions were raised by stakeholders, specifically health care providers, clinical laboratories, test developers, pharmaceutical companies, and payers. Because drug development and test development have very different characteristics, questions were raised about timelines, required resources, market protection, intellectual property, market size, and potential profits. In some cases, as noted by Walter Koch of Roche Molecular Systems, companies have not submitted an IVD for approval from FDA because the return on investment would not justify the effort needed to gain approval. Also, according to John Pfeifer of the Washington University School of Medicine, limited tissue samples may prohibit performing multiple tests for the same disease or for different diseases in clinical laboratories.

Another major concern is that the regulatory pathway remains uncertain for LDTs. The laboratories in which LDTs are used are governed by CLIA for analytical validity and are at the regulatory discretion of FDA. CLIA is administered by the Centers for Medicare & Medicaid Services (CMS) to federally regulate laboratory testing on humans in the United States (with the exception of testing for research purposes).

continued

BOX 1-1 Continued

While FDA regulates IVDs, historically it has used discretion in its regulation of LDTs. Clinical laboratories and laboratories in pathology practices and university medical centers develop, validate, and use LDTs. Furthermore, if an FDA-approved test is modified and improved by a CLIA laboratory, it is considered an LDT.[a] CLIA sets standards for analytical validity and quality assurance for LDTs, but, according to Scott Patterson of Amgen, a major question for stakeholders is whether LDTs have the same assurance of performance characteristics as an IVD approved through the FDA co-development process.

[a] Clinical Laboratory Improvement Amendments. http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia (accessed on November 26, 2013).

Since 2009 the Roundtable on Translating Genomic-Based Research for Health has focused much of its work on examining these issues and the development of clinical utility data for genomic technologies because establishing utility is one of the major obstacles to translating sequencing technology for patient use, said Robert McCormack, workshop co-chair and head of technology innovation and strategy at Veridex LLC. Because of the need to further address the questions surrounding the companion diagnostics co-development process (see Box 1-2), the Roundtable held a workshop on February 27, 2013, in Washington, DC, with the objective to examine and discuss challenges and potential solutions for the co-development of targeted therapeutics and companion molecular tests for the prediction of drug response.

Prior to the workshop, key stakeholders, including laboratory and medical professional societies, were individually asked to provide possible solutions to resolve the concerns raised about co-development of companion diagnostic tests and therapies (see Box 1-2). Workshop speakers were charged with addressing these solutions in their presentations by providing insight on (1) whether the proposed solutions address the problems described, (2) whether there are other solutions to propose, and (3) what steps could be taken to effectively implement the proposed solutions.

WORKSHOP THEMES

The next four chapters of this summary of the workshop offer perspectives from a variety of stakeholders on the co-development of drugs and diagnostics. Chapter 2 provides perspectives on FDA's approach to the co-development process from inside and from outside the agency. The changes

BOX 1-2
Concerns Identified by Individual Stakeholders and Potential Solutions to the Current Co-Development Process

Common Stakeholder Concerns

- Regulatory uncertainty around LDTs.
- Reimbursement uncertainty with regard to LDTs and future generations of tests.
- Erosion of investments and of the clinical utility of the original device as additional tests emerge on the market.
- Clinical difficulties for demonstrating clinical utility of multiple companion diagnostics for the same drug.

Potential Stakeholder Solutions

- The regulatory pathway for co-developed tests needs to be clarified for both pre- and post-therapeutic approval, including a pathway for tests to be developed for off-label use of drugs when such use is recognized as a standard of care in medical practice. Developers (whether industry or laboratories) of new tests or new versions of established co-developed tests should offer proof of the clinical validity of these versions in order to obtain coverage. Coverage and reimbursement should be based on the performance of each unique test and the evidence that supports it. (Coalition for 21st Century Medicine)
- The role of CLIA should be strengthened to assure the clinical validity of laboratory tests. A test registry should be established to improve the transparency of public information, and efforts should be directed at expanded oversight of genetic tests directly marketed to consumers. (American Clinical Laboratory Association)
- Tests should be regulated according to risk instead of according to the business model for test development. (Advanced Medical Technology Association, AdvaMed)
- The relevant analyte for drug efficacy rather than the specific test should be defined. Test submission should include enough details about the biologic basis for the test and its performance characteristics that these could be used as benchmarks for comparison of other tests. A repository for test results would allow a more rapid assessment of the clinical usefulness of testing. (College of American Pathologists, CAP)
- A better understanding of tumor biology and drug–target interactions involved in the use of a predictive biomarker is needed before a predictive biomarker is selected for development and validation. Regulatory certainty regarding FDA oversight of LDT companion diagnostics is needed, with coordination between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health. (American Society of Clinical Oncology, ASCO)
- The cost of the test should be included in the price of the drug so that the laboratories would be committed to using that specific test for the drug. (individual participant submission)

in drug development strategies necessitated by companion diagnostics are discussed along with commercial challenges such as available resources and mismatched market sizes.

Chapter 3 summarizes the observations of representatives from three different end user groups: patients, health care providers, and clinical laboratories. Challenges for clinical labs, the regulation of NGS, and patient-centered efforts are addressed. Chapter 4 offers the views of representatives of pharmaceutical companies. Several workshop participants pointed to what they called "the problem of the generic"—that is, once an IVD has been approved, little prevents clinical laboratories from offering a test for the same analyte at a reduced cost. This undercuts the economic incentives to develop IVDs and the performance characteristics of LDTs compared with FDA-approved IVD.

Chapter 5 focuses on the regulatory environment for the marketing of co-developed companion diagnostics, the regulatory scrutiny that should be given to IVDs and LDTs, demonstrating the safety and effectiveness of devices, and reimbursement decisions based on clinical utility.

Finally, Chapter 6 outlines observations made by individual speakers and workshop participants about the possible solutions in Box 1-2 for addressing the current co-development landscape. Regulatory considerations are discussed, including a role for FDA to regulate tests based on risk, making CLIA more robust for LDTs, and choosing one regulatory pathway for all co-developed companion diagnostic tests to ensure their safety and effectiveness. The chapter reviews how standards of evidence for clinical utility are defined, as well as the pricing of tests. The role of NGS in the context of test regulation and reimbursement for more comprehensive diagnostics was not a focus of the workshop, but several speakers addressed these issues as they may be important in the future.

2

Regulatory Perspectives

Important Points Highlighted by Individual Speakers

- The draft guidance on companion diagnostics from FDA recommends developing both the test and the drug together, which creates a new opportunity for developers to work and learn together to more clearly define a process and to coordinate a timeline for development.
- The performance of a companion diagnostic is closely tied to the performance of the associated drug, and this relationship is essential for determining the safety and effectiveness of the products for patient use.
- The major challenge for co-development is more commercial than regulatory because there are inherent differences in developing tests and drugs, including mismatched markets and resources.
- Combining the cost of a test and a drug may provide a solution for aligning market differences and accelerating regulatory approval and reimbursement decisions for two different products.

Speakers discussed regulations from the perspective of FDA and of an entrepreneur with a focus on personalized medicine, in the context of the current co-development process for tests and drugs. Elizabeth

Mansfield, director of the personalized medicine staff in the Office of In Vitro Diagnostics and Radiological Health at FDA, described the historical development of FDA's policies for companion diagnostics and the main features of the companion diagnostic draft guidance. Felix Frueh, entrepreneur-in-residence at Third Rock Ventures, commented on some of the issues those policies raise. Together, they presented an overview of co-development of tests and therapeutics and outlined the challenges of and potential solutions to these issues.

OVERVIEW OF CO-DEVELOPMENT AND COMPANION DIAGNOSTIC POLICY

The concept of companion diagnostics is not new, Mansfield said; testing for estrogen and progesterone receptor expression has been done since the 1990s to determine if a patient would benefit from hormone therapy in treating breast cancer. In 1998 FDA approved the use of the drug Herceptin in patients with breast cancer who tested positive for human epidermal growth factor receptor 2 (HER2), one of the earliest examples of a co-development companion diagnostic model before there was a formal process in place. When Herceptin was approved for use in patients with metastatic breast cancer, FDA also approved a test to examine HER2 levels. One reason for having a test was to decrease risks, Mansfield said, and Herceptin's cardiotoxic side effects are now well known. In the case of the drugs Selzentry and Tykerb, which were approved in 2007 and whose use depends on test results, a companion diagnostic policy was not yet in place when they were approved and FDA did not apply the policy retroactively.

Recognizing that tests can be drivers of therapy, FDA began to develop guidance to reflect drug development strategies that account for genetic information. It held public discussions about pharmacogenomics, requested voluntary genomic data submissions, and addressed other issues concerning the use of genomic data to guide drug development, Mansfield said. FDA realized that a policy was needed to protect patients while also allowing companies to plan for the development of tests that would support therapeutic approval, she said. FDA also realized that companies want predictability in the regulatory process.

Companion diagnostics are tests, Mansfield emphasized, but the test performance is closely tied to the performance of the associated drug. Thus, knowledge about the test is essential to understand the safety and effectiveness of the drug. Tests for the same analyte can differ, sometimes significantly. The technology, cut-off levels, and performance can all vary, and different tests are likely to identify different populations. "You want to know all of these parameters before you decide on which test is going to be used," Mansfield said, "and if you want to use multiple tests [you will need

to know] how these different performance parameters compare and affect the outcome [because] test performance actually makes the drug performance." All of this information is needed to determine which patients will benefit from the drug and how to adequately label a drug.

In July 2011 FDA released a draft guidance document for industry and FDA staff on IVD companion devices and held a 90-day comment period, Mansfield said. At the time of the workshop, FDA expected to release the final version of the guidance soon. Mansfield reviewed a few key pieces of the policy. First, the policy defines an IVD companion device as "an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product." Such a diagnostic could identify a population for efficacy, for safety, or for other purposes. The document also differentiates companion diagnostics from diagnostics used for other purposes. Thousands of diagnostic tests have been cleared or approved, but only perhaps 15 companion diagnostics had been approved (see Table 2-1) at the time of the workshop, Mansfield said.

TABLE 2-1 FDA-Approved Companion Diagnostic Devices

Drug (trade name)	Device (trade name)	Intended Use
Erbitux	*therascreen* KRAS RGQ PCR Kit	Real-time qualitative PCR assay used for the detection of seven somatic mutations in the KRAS in colorectal cancer tissue.
Erbitux, Vectibix	DAKO EGFR PharmDx Kit	Qualitative immunohistochemical assay to identify EGFR expression in normal and neoplastic tissues and as an aid in colorectal cancer tissue.
Exjade	Ferriscan	Measures liver iron concentration to aid in the identification and monitoring of non-transfusion dependent thalassemia patients.
Gilotrif	therascreen EGFR RGQ PCR Kit	Real-time PCR test for exon 19 deletions and exon 21 (L858R) substitution mutations of EGFR in NSCLC tumor tissue.
Gleevec/ Glivec	DAKO C-KIT PharmDx	Immunohistochemical assay for the identification of c-kit protein/CD117 antigen expression in normal and neoplastic tissues and as an aid in diagnosing gastrointestinal stromal tumors.
Herceptin	INFORM HER-2/ neu	FISH DNA probe assay for HER2/neu gene amplification in human breast tissue as an aid to stratify breast cancer patients. Also indicated for use in breast cancer in patients.

continued

TABLE 2-1 Continued

Drug (trade name)	Device (trade name)	Intended Use
Herceptin	PathVysion HER-2 DNA Probe Kit	Detects amplification of the HER2/neu gene via FISH in breast cancer tissue specimens.
Herceptin	PATHWAY ANTI-HER-2/NEU (4B5) Rabbit Monoclonal Primary Antibody	IHC test for c-erbB-2 antigen in normal and neoplastic tissue. Indicated as an aid in the assessment of breast cancer patients.
Herceptin	InSite HER2/neu kit	IHC assay for the over-expression of HER2/neu (i.e., c-erbB-2) in normal and neoplastic tissue sections. Indicated as an aid in the assessment of breast cancer patients.
Herceptin	SPOT-Light HER2 CISH Kit	CISH for HER2 gene amplification in breast carcinoma tissue.
Herceptin	Bond Oracle HER2 IHC System	Immunohistochemical assay to determine HER2 oncoprotein status in formalin-fixed, paraffin-embedded breast cancer tissue.
Herceptin	HER2 CISH PharmDx Kit	In situ hybridization assay for the HER2 gene and centromeric region of chromosome 17 for breast cancer tissue specimens.
Herceptin	INFORM HER2 DUAL ISH DNA Probe Cocktail	In situ hybridization assay for HER2 gene status by enumeration of the ratio of the HER2 gene to Chromosome 17 in breast cancer tissue specimens.
Herceptin, Perjeta	HERCEPTEST	Immunocytochemical assay to determine HER2 protein overexpression in breast and gastric cancer.
Herceptin, Perjeta	HER2 FISH PharmDx Kit	FISH assay for HER2 gene amplification in breast cancer tissue specimens and specimens from patients with metastatic gastric or gastroesophageal junction adenocarcinoma.
Mekinist; Tafinlar	THxID™ BRAF Kit	Qualitative detection of the BRAF V600E and V600K mutations in melanoma tissue.
Tarceva	cobas EGFR Mutation Test	Real-time PCR test for exon 19 deletions and exon 21 (L858R) substitution mutations of EGFR in NSCLC tumor tissue.
Xalkori	Vysis ALK Break Apart FISH Probe Kit	FISH for ALK gene rearrangments in NSCLC tissue specimens.
Zelboraf	cobas 4800 BRAF V600 Mutation Test	Real-time PCR test for BRAF V600E mutation in melanoma tissue.

NOTE: CISH, chromogenic in situ hybridization; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; PCR, polymerase chain reaction.
SOURCE: Modified from FDA Companion Diagnostic Devices: In Vitro and Imaging Tools, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm (accessed October 16, 2013).

Second, the policy calls for contemporaneous approval of the therapeutic and the companion diagnostic, Mansfield said. "If we approve a test without drug approval, then the test has no legitimate intended use. If a drug is approved without the test, then it is likely that the test wasn't needed." The exception to this policy, she said, is that if a therapy is meeting an unmet need, the drug can be approved first with the test approval following soon after so as to not hold up the approval of therapies for diseases that do not have alternative treatment options. FDA has no preference for the manufacturer of a particular test; sponsors determine which test will be submitted for approval. This has led to a learning experience for both test developers and drug developers, Mansfield said, because "these two sectors have not been very familiar with each other." But the situation is changing, in part because some pharmaceutical companies are creating small diagnostic enterprises to support their personalized medicine efforts.

Mansfield further clarified the labeling policy for therapeutic products. The label refers to "a type of approved or cleared IVD companion diagnostic device, not a specific one by name," she said. While the test can be named elsewhere in the label, it will not be named in the indications, warnings, or precautions sections. This is to account for the fact that better tests may be approved at a later date, a possibility that FDA wanted to account for, Mansfield said. As the policy states, "This will facilitate the development and use of more than one approved or cleared IVD companion diagnostic device of the type described in the labeling for the therapeutic product." Also, putting the test name in the label would essentially make the drug–test pair a combination product, which falls under a different category of regulation at FDA. A rare exception to this would be when only one test can be used with the drug.

FDA is also considering what the process will be for follow-on tests and how to account for new information for already-approved therapies. It does not foresee being able to apply a single approach to all follow-on tests, Mansfield said. The biggest concern for such tests is that the population tested in seeking approval for the test would be biased to make the test perform better than it would in practice. Generally, the process for follow-on tests involves an analytical comparison, but samples with clinical outcomes typically are not available. Once a drug is approved, it is unethical or unworkable to run a trial to generate clinical trial specimens with clinical trial outcomes. "Those specimens are essentially gone, and you have to start with a different type of specimen," she said. As a result, many of the considerations in approving such a test involve the specific test and specific drug. Mansfield added that regardless of whether the test is a follow-on or the initial development, premarket approval is still needed because of the high risk of harm. In contrast, the labeling of the companion diagnostic will list the name of the drug, Mansfield said. The users of the drug need

to know which test to use, and the performance characteristics of the test in the label are generally derived from the therapeutic trial of the drug.

The use of a test in a therapeutic trial is often investigational. In such cases, the risk of use must be determined, and significant risk requires a submission to FDA to ensure safety, regardless of the manufacturer of the test or whether the test is in use. The development of a test is often exempt from investigational regulations, but when the test is used in therapeutic trials, it may not be, Mansfield said. This risk assessment applies to LDTs and tests made by IVD manufacturers, she added.

Mansfield also addressed why certain drugs did not have a companion diagnostic approved together under the policy. She explained that, for example, Kalydeco, a drug that works well in patients with cystic fibrosis who have a particular mutation, was approved by FDA without a companion diagnostic. In the case of cystic fibrosis, 95 percent of patients have a genetic mutation panel performed at the time they are diagnosed, so they already know their mutation status and therefore do not need to be retested to determine whether they should be placed on Kalydeco (ACOG, 2011). Even for Kalydeco's clinical trial, the patient's medical record was used to determine their mutation status.

FDA also has been working on guidance for the co-development process, Mansfield said, but the guidance has been difficult to write because of the programs that the agency has reviewed so far, no two co-development programs are the same. Both industry and FDA are gaining experience as the policy is defined, Mansfield said. Most of the general principles in the guidance have been drafted, and Mansfield said she hoped that it would be out to the public within the year. The guidance will likely discuss both therapeutic and diagnostic programs with an emphasis on the diagnostic process.

Other non-IVD diagnostics are also being considered as companion diagnostics. An example is the recent approval of Exjade, a drug used to treat non-transfusion-dependent thalassemias and its companion radiological test to measure liver iron concentration.

As FDA and industry have increased their knowledge and experience with the co-development of diagnostics and therapeutics, the approval process has become smoother, Mansfield concluded, but questions remain, and new ones arise every day.

UNDERSTANDING CO-DEVELOPMENT

In the context of co-development, effectiveness means that a drug or test is adequate to accomplish a specific purpose, produces the intended or desired result, and is actually in operation as opposed to just having the potential for use, Frueh said. For a product to be approved by FDA, effectiveness needs to be demonstrated, so it is primarily a regulatory concern.

By contrast, efficacy refers to the power or capacity to achieve the desired effect under ideal conditions, and it is more of a concern for payers. For example, Frueh said, in a clinical trial inclusion and exclusion criteria create a more idealized situation than would be encountered outside of this environment. Co-development is the "development of a test with a drug to make the use of the drug more effective or safer," he said. "It really is a method to make medicine more precise." Co-development is not an approach to make a clinical trial less costly, nor is it a way to accelerate the time it takes to bring a product to market, Frueh said. Co-development is also not a biomarker discovery tool, he said, because "by definition you have to know your marker and you have to know what you're using it for; only that allows you to create a strategy to align the development of the marker with the drug."

Hurdles to Co-Development

The co-development of a diagnostic and a therapeutic is not a regulatory issue, Frueh said. "I do not believe these regulatory hurdles exist." In fact, he said, FDA is helping with accelerated approvals, as in the cases of Xalkori, Kalydeco, and Incivek. The most significant obstacles that need to be dealt with involve business development and reimbursement issues. "Drug development and test development are inherently difficult to coordinate," Frueh said. "For the most part, the timelines of the two businesses really do not align. The resources are completely mismatched, and the market protection between the drug and the diagnostic is entirely different." The underlying differences result from the differences in markets between drugs and tests. Drugs typically involve high-risk investments and high rewards, he said, while tests make up a significantly smaller fraction of the market and come with moderate to high risk and low rewards. As a result, Frueh said, there is less interest in investing in medical devices and IVDs because they are not as lucrative as making an investment in pharmaceuticals.

In order to explain the return on investment for a test, Frueh provided a detailed scenario. A $500 test intended to be used by a population of 1 million represents a potential market of $100 million if the test is able to reach 20 percent of the population. If the profit margin is 50 percent, then an initial investment of $100 million would be recovered in 2 years. If such a test took 4 years to develop, it would start to make a profit after 6 years. A modest return on investment would be three times the original amount invested, Frueh said, or $300 million in the case of this hypothetical test. Thus, this test would take 12 years to produce the desired return on investment, which represents a 9.5 percent annual rate of growth of capital. "This doesn't necessarily sound unreasonable," Frueh said, "but it's not really

something that gets venture capitalists overly excited." Because these tests produce a relatively low return on investment—at least from the point of view of venture capitalists—the diagnostic market is relatively unattractive to investors.

Some new drugs are currently priced at record levels; for example, the price of Xalkori is approximately $115,000 per patient per year, and other new drugs are also extremely expensive, Frueh said. Yet the cost of the *EML4-ALK* companion diagnostic test that is required for the use of Xalkori is reimbursed at $128.48,[1] and diagnostic companies are under pressure to reduce prices further. As a result, the disparity between drug and diagnostic prices is increasing, and the goals of drug development tend to dictate the goals of the test development in a co-development effort. Not every diagnostic will progress all the way to the market, nor will the price for the test necessarily be the same 12 years after development begins. "The reality is that the rewards and stakes for drug development are significantly higher than they are for test development," Frueh said. "This is not a relationship between two equal partners." As knowledge grows, new markers might be developed, requiring the development of a new test. But the developer does not necessarily have market exclusivity or intellectual property protection; another group could develop a different diagnostic for the same marker and acquire part or all of the market.

Potential Solutions for Co-Development

The critical consideration for a test or drug is the resulting health outcomes, Frueh said. If a test adds to the effectiveness of a therapy, the test has inherent value. Furthermore, the difference in the effectiveness of a drug with the test versus without the test is a measure of the value of the test. Co-development also is aligned with payers' current demand for more evidence of positive outcomes. Furthermore, payers view such tests as a way to control costs. To capture the value of the test in the payment, Frueh said, "if you get a product that doesn't work, you also don't really want to pay for it. . . . Yet we do it every day in the health care system. I think we need to get out of this loop and really look at what works."

If payments were for outcomes rather than the products, then the value, taking into account both the test and the drug, could be reflected in the payment. In that case, Frueh said, it would make sense to pay for the test and drug together, which then raises a reimbursement issue. Combining the cost of a test and a drug (see Box 1-2, individual participant submission)

[1]CGS Administrators, Molecular Pathology Reimbursement for Dates of Service 01/01/13–09/30/13, http://www.cgsmedicare.com/ohb/coverage/mopath/mopath_reimbursement.html (accessed October 16, 2013).

would make it easier to justify the initial expense to develop the tests. This approach would provide the outcome evidence that payers need, and it also would accelerate regulatory approval and reimbursement.

Such a change would not be easy to make, Frueh acknowledged. But combining the costs for a test and a drug would contribute to an ongoing shift in thinking about regulatory and payer issues from a static paradigm to a more dynamic state, he said (see Figure 2-1). Incorporating reimbursement considerations into strategies for trial designs would improve both efficacy and effectiveness, thus serving the interests of both regulators and payers. The drug industry and diagnostic industry would be more equal, so that they could continue to interact together with FDA during the approval process. This team approach to co-development would help align the two industries, Frueh said.

Two models could incentivize co-development of drugs and diagnostics, Frueh said. The first would be for those involved in early test development so that their investment would be fully compensated by pharmaceutical companies. In this scenario, the drug company would assume the financial responsibility for the test development. Second, a revenue-sharing model could be considered in which a percentage of the drug revenue is generated from sales based on decisions made using the test, Frueh said. This model would reflect a partnership between the two development sectors.

NEXT-GENERATION SEQUENCING

During the discussion, Mansfield, Frueh, and individual workshop participants considered the potential roles of next-generation sequencing in disease diagnosis and in affecting outcomes. Genomic information could have both prognostic value and, in some cases, predictive value for a therapeutic. The use of next-generation sequencing as a diagnostic will require work and discussion with potential sponsors, Mansfield said. Some devices are complicated in that they have more than one indication, such as prostate-specific antigen (PSA) tests for monitoring cancer, which are classified as a Class II device, and PSA tests for diagnosis, which are classified as a Class III device. In the case of molecular diagnostics, genomic information will point toward therapies for which no indication in a drug label exists, which is a much bigger regulatory challenge, Frueh said. "The sheer magnitude of the information that we'll find on the genetic and molecular level is going to far surpass our capacity to run clinical trials," he said. In fact, perhaps clinical trials will not be needed, especially because clinical trials cannot be run for every marker and every condition. But the same mutation is not always the driving factor for different cancers, said Walter Koch, vice president of global research at Roche Molecular Systems, and a workshop speaker. In contrast to Frueh's view, Koch said that only through clinical

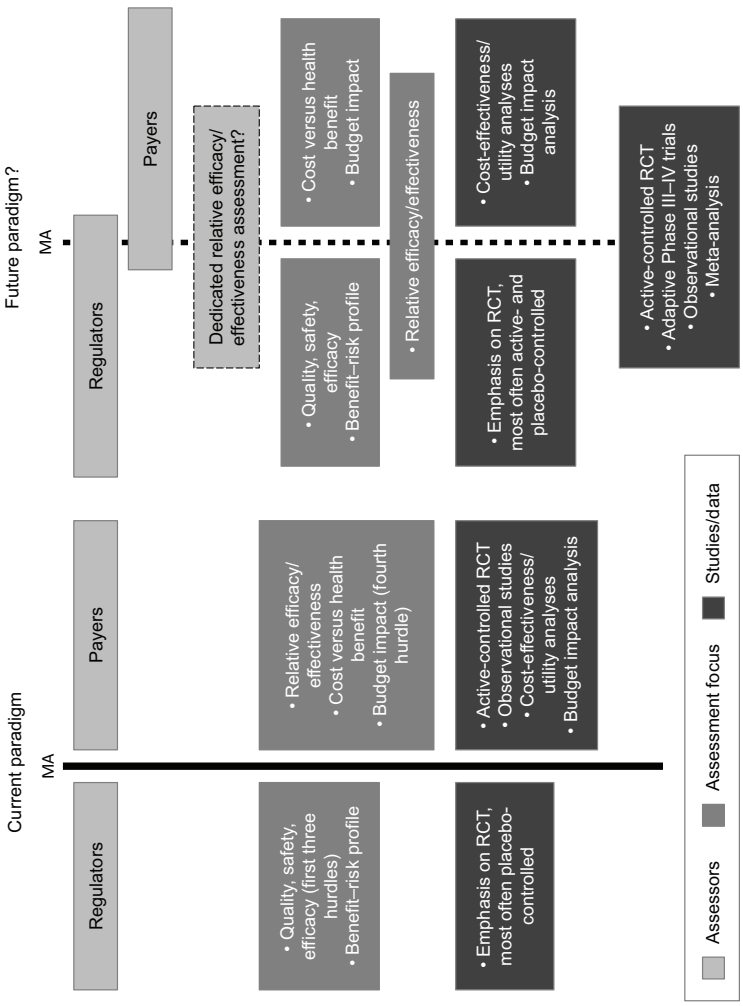

FIGURE 2-1 Integrating regulatory agencies and payers for product development.
NOTE: MA, marketing authorization; RCT, randomized controlled trial.
SOURCE: Reprinted by permission from Macmillan Publishers Ltd.: Nature Reviews Drug Discovery (Eichler et al., 2010), copyright 2010.

trials can a drug target be validated by showing that the drug produces better outcomes. Next-generation sequencing will find many variants, but they will not always be targets for a particular disease, he said.

Speaking for herself and not on behalf of FDA, Mansfield stated that medicine is heading toward next-generation sequencing, which is "the ideal place to be," she said. "When you get diagnosed, you get a test, and we have all the information on the table from a single test." In that case, the test may be quite general as opposed to being used as a companion diagnostic to provide usage information about a single targeted therapy. In the future, next-generation sequencing could report only mutations that have known drug safety or efficacy correlations, Mansfield said, with additional data being retained for investigational use. As new information becomes available, new drugs could be approved, which would greatly increase the efficiency of the approval process. But, she said, "even in co-development . . . not everybody who has [a particular] marker actually benefits from the drug. So we're still not there yet, even with next-generation sequencing. To the degree that subclassification actually improves that, that's great. But I think we can't just assume that because you have a mutation, you're going to get benefit from the drug because we know the opposite."

3

Perspectives from Patients, Providers, and Laboratory Representatives

Important Points Highlighted by Individual Speakers

- Implementing a learning health care system would allow for sharing of test data, save time and resources, and add value by facilitating a focus on patient outcomes.
- A flexible regulatory process for utilizing next-generation sequencing for routine screenings will allow for a hypothesis-generating approach to diagnosis and treatment of patients.
- Requiring that LDTs demonstrate their equivalence to IVDs through rigorous proficiency testing could establish uniformly high standards for companion diagnostics.
- Next-generation sequencing will require a new approach to thinking about clinical trial designs, because every patient will in essence have to be treated as unique.

A variety of individuals use companion diagnostics and the results of these tests, including patients, health care providers, and clinical laboratory employees. Representatives of each of these three end-user groups described the value and problems with co-developed companion diagnostics along with the changes that can be expected as next-generation sequencing becomes a more prominent part of clinical practice.

FOCUS ON PATIENTS

Thinking about patients at the beginning of the process rather than at the end focuses the discussion on outcomes, said Sharon Terry, president and chief executive officer of Genetic Alliance. Patients should not be considered just the end users of genetic tests.

From the patient perspective, health care providers do not always have a clear sense of what is most useful to patients. Providers may overtreat, undertreat, inappropriately treat, or not treat at all, based on the available information. What insurance will cover is often unclear, which can lead to disagreements over what should and should not be prescribed or performed. Patients also may make demands, some of which are appropriate and others of which may be inappropriate. "None of these are clear-cut," Terry said.

A fundamental problem, Terry said, is that the incentives to understand disease are low. Medicine is focused on trying treatment after treatment, but what is not captured during that process are data that could be used to determine what is effective and what is not effective. The key problem is finding an incentive to have a greater understanding of the biology of the disease, Terry said. What group will enforce assessments of value based on outcomes? In other industries, the consumer is empowered to do this, Terry noted, but in medicine, "all the stakeholders, including patients, make decisions that are disconnected from the consequences." Developing companion diagnostics may even be an interim solution toward what is actually needed for understanding disease. There may be no need for a companion diagnostic after acquiring this information, she said.

Learning Health Care System as a Potential Solution

To address the difficulty of thinking on a systems level about patient care, the nation needs a learning health care system, Terry said. This will enable people to "understand the disease, the progression of the disease, the treatment, and the reaction to the treatment, adverse or not." In short, she said, a learning health care system "will help us to understand the outcomes that we seek." Similarly, transparency in the performance of tests, the data generated by those tests, and the consequences of those tests can lead to best practices that can be shared within the system, which can save time and money. This new way of thinking about the health care system involves all stakeholders and provides an opportunity to create new metrics and new value chains tied to outcomes. People have to be willing to risk what those who are sick risk every day, which is changing the model, finding a new solution, and possibly destroying a current business model, she said. That will be difficult in medicine, particularly given the lack of empowerment among the people who receive care.

Terry read a quote from the book *How We Do Harm: A Doctor Breaks Ranks About Being Sick in America*: "Proponents of science as a foundation for health care have not come together to form a grassroots movement, and until this happens, all of us will have to live with a system built on pseudoscience, greed, myths, lies, fraud, and looking the other way" (Brawley and Goldberg, 2012, p. 27). "That's pretty harsh, but I think it's real and true," Terry said. Health care is going to have to be like a civil rights issue, she said. People have a right to demand not just tests and treatments, but also solutions to the health problems they confront.

USE OF TESTS IN ONCOLOGY

In oncology, biomarkers are used for a variety of purposes, including diagnosis, prognosis, and predictions of response, toxicity, risk of secondary cancers, and familial risk, noted Mark Robson, clinic director of the clinical genetics service in the Department of Human Genetics at Memorial Sloan-Kettering Cancer Center. Biomarkers also take a variety of forms and use different technologies, including imaging, immunohistochemistry, and somatic or germline DNA sequencing. Companion diagnostic tests have been used for testing hypotheses rather than generating hypotheses, and this has significant implications for study design when trying to evaluate the benefit of the tests, Robson said.

The main clinical problem, Robson said, is that no matter how good a biomarker is, the concordance between the biomarker and drug response is often incomplete. The state of a biomarker is just one piece of information in a much broader assemblage which includes such factors as the extent of disease and the results of prior therapies. This complex picture makes it difficult to assess the clinical utility of a test, which essentially becomes "a value judgment," Robson said, and a matter of defining what makes the test worth using. "There doesn't seem to be a consensus about the kinds of metrics that we should use to establish sufficient clinical validity or sufficient clinical utility to allow us to progress forward," he said. Is overall survival more important than progression-free survival? What endpoints should be used? Are thresholds important? Those working on drug development have had these conversations for a long time, Robson said, and these discussions should be explored as they pertain to companion diagnostics as well.

It is also not clear which trial designs are optimal for answering the sorts of questions that Robson raised about clinical validity and utility. Requiring randomized controlled trials may set too high a bar for several reasons, Robson said. In small subsets of patients, it is challenging to "design statistically robust studies without screening thousands and thousands of patients, which then becomes fiscally impossible," he said. Furthermore, the randomized controlled trial population may not reflect

clinical reality. From a clinician's standpoint, Robson concluded, the major challenge is delineating clinical validity and the utility of a companion diagnostic in a way that informs clinical decision making in real-world circumstances. Some of the stakeholder solutions address that challenge, but they do not fix it.

In silico methods that are used to predict functional responses to therapies can be useful, but the data are not always publically available, Robson said. If a laboratory collects and analyzes data but does not publicly release those data, other groups may waste time and resources studying a question that has already been answered. Also, the use of *in silico* methods to predict response may be application specific. This method may work where treatment response is dependent upon loss of function—for instance, with *BRCA* mutations and PARP inhibitors—but it will not necessarily be useful in more complicated settings.

In oncology, sample composition offers additional diagnostic and treatment challenges, including the sample consisting of an admixture of tumor tissue with normal tissue, tumor heterogeneity, and the evolution from primary tumor to metastasis. As Robson said, "Different tests from different sites and different points in a patient's journey may have different meaning, and that needs to be accounted for."

Today, the clinical approach to treatment is fairly linear and based on hypothesis testing, Robson said. For example, after reviewing the clinical data for a patient, an oncologist may order a test for the BRAF V600E mutation to determine whether the patient is a candidate for Zelboraf, and then a decision is made concerning the appropriate treatment on the basis of that test. This model could evolve to account for NGS by using the technique to gather data from the patient to generate hypotheses, not test them. The extra information that is obtained is part of the patient evaluation and should therefore be reimbursed, Robson said. The regulatory process that is established for companion diagnostics should be flexible so as to allow for the future accommodation of routine screening using next-generation sequencing.

CHALLENGES FOR CLINICAL LABORATORIES

Patient care occurs in a world that is far from ideal, said John Pfeifer, vice chair for clinical affairs, pathology, and immunology and professor at Washington University School of Medicine. For example, patients present with advanced rather than early disease, and sometimes they do not adhere to treatment protocols. Health care providers and clinical laboratories have to deal with many such issues every day, Pfeifer said.

Clinical laboratories have a different set of issues than health care providers, Pfeifer continued. First, the laboratories typically face limitations in

the quantity of tissues available for testing. Pfeifer's laboratory is a "full-service genetics laboratory" which performs tests from conventional cytogenetics to next-generation sequencing. A typical PCR-based test, whether a uniplex or a multiplex test, requires in the range of 25 to 50 nanograms of DNA, Pfeifer said. Many times in routine clinical practice, only small samples are available from biopsies or fine needle aspirates. About 7 percent of cases have less than 100 nanograms of DNA, 12 percent have less than 200 nanograms, and another 30 percent have between 200 and 750 nanograms, Pfeifer said. As a result, laboratories generally need to make decisions about which tests they are going to perform.

Laboratories also face demands for testing of numerous loci from the same specimen. For example, a patient who presents with non-small-cell lung cancer needs a number of loci tested for first-line therapy, including those for *ALK*, *BRAF*, *EGFR*, *PTEN*, and *RAS*. Limits on the amount of test substrate can have a major impact on the testing that is actually performed. Similarly, requirements for slide-based assays, such as interphase fluorescence in situ hybridization (FISH), further constrain testing, Pfeifer said, because producing samples to do such assays reduces the amount of tissue available for other tests. Another challenge with tissue samples is that the type of sample and the preparation needed for a companion diagnostic test may not always align with the type of sample that is most non-invasive to obtain and that makes most sense from the patient care perspective. If the sample was preserved in ethanol or methanol instead of formalin, it may be less amenable to companion diagnostic tests. Cost considerations that are taken into account for testing are also concerns, Pfeifer said. For example, one way to reduce costs is to bring a patient into a cytology clinic and perform a fine-needle aspiration sampling of a lymph node rather than to operate on a patient and perform an excisional biopsy. Rapid advancements in technology and improved understanding of disease also affect testing. For example, new evidence may indicate that a mutation involved in one disease appears to be involved in a different disease as well, whether for diagnosis or treatment. This raises the question, In what circumstances should that mutation be tested?

Formal Regulation of LDTs

"Companion diagnostics have put the clinical laboratory in a very difficult position," Pfeifer said. "We're in a catch-22. On one hand, there are companion diagnostics that have been approved for testing specific patient populations, but by definition, they are not applicable to a lot of the clinical testing that laboratories are asked to do, based on current paradigms. . . . So we are forced to use that companion diagnostic as an off-label use or an LDT." But in some cases, it is advised to pursue a companion diagnostic

model because the LDT is not appropriate for the testing. "Which model is it?" Pfeifer asked. FDA does not have the resources to regulate LDTs, he said, but LDTs need to be regulated. LDTs exist in part because the companion diagnostic model is not comprehensive. Thus, Pfeifer said, one option would be to change the paradigm by requiring demonstration of the equivalence of LDTs with FDA-approved IVD companion tests through rigorous proficiency testing.

This proficiency testing requirement would cut both ways, Pfeifer said. An LDT will need to meet the standards of the approved companion diagnostic test, although Pfeifer stated that "plenty of laboratories hold themselves to a higher standard and will only use an LDT if it meets the standard of the companion diagnostic." At the same time, a companion diagnostic is only as good as the laboratory using it. Regulatory oversight of LDTs should be formalized, Pfeifer said, adding that using CLIA, which is an established paradigm, would be the fastest and easiest way to do so because the pathway is already defined.

Response to Potential Solutions

Pfeifer responded to the stakeholders' suggested solutions for improving the current companion diagnostic model as outlined in Box 1-2. The American Clinical Laboratory Association proposal recognizes that LDTs are part of the genetic testing landscape and proposes a regulatory framework consistent with the precedent for other types of laboratory testing. A disadvantage to this proposal is that it would apply to the direct-to-consumer market, in which health care providers are not involved in the testing for inherited mutations, Pfeifer said. What does this model look like, Pfeifer asked, when the patient-doctor relationship is removed?

Today, most companion diagnostics separate patients into two categories—responders and non-responders. But when genetic tests are used to examine hundreds of thousands of genes, patients will be grouped into smaller and smaller categories. Eventually, every patient will have to be treated as unique. This will require a radically different approach to clinical trial designs, along with bioinformatics solutions and statistical tests to validate tests that apply to more than one disease, Pfeifer said.

IMPLICATIONS OF NEXT-GENERATION SEQUENCING

The presenters and workshop participants continued to explore the possible effects that the application of next-generation sequencing for whole genome or whole exome sequencing could have on genetic testing and on disease classification. "Patient-centeredness is at the heart and soul of the modern era of stakeholder engagement," said Muin Khoury, director of

the Office of Public Health Genomics at the Centers for Disease Control and Prevention, in agreement with Terry. He said that he hoped that stratifying patients by disease into treatment groups would be more like "*n* of a few" as opposed to a single subject "*n* of 1" classification. The *n* of 1 situation is a potentially intractable problem, he said, because it is not clear how the principles of evidence-based medicine would apply to this situation. Khoury said that he preferred to think about stratified medicine rather than personalized medicine so that there are a manageable number of subgroups for each disease. If that is not the case and each person is unique, then the rare disease model of regulation would apply. There is also a need for general methodology, or at least for an intellectual framework, to delineate what sequence alterations potentially predict response, and because directly evaluating every single sequence variant as small *n* of 1 clinical trials is not feasible, Robson said, "we need some creative thinking about designs." Evaluation of Genomic Applications in Practice and Prevention, along with other groups such as the Clinical Sequencing Exploratory Research consortium, Blue Cross and Blue Shield Association Technology Evaluation Center, and Kaiser Permanente, serve as reviewers of the evidence base.

Pfeifer called attention to the need to anticipate the coming era of next-generation sequencing. Next-generation sequencing technology will solve some of the current problems associated with regulation and reimbursement. It will be able to identify all four major categories of genetic mutations: single-nucleotide variants, small insertions and deletions, copy number variants, and large-scale structural variants such as translocations and inversions. The technology will allow for the testing of hundreds or thousands of genes with the same amount of analyte, and it will be markedly less expensive than running many individual tests. Pfeifer's laboratory already has started doing next-generation sequencing because some clinical settings and specimen types call for the use of that technology. The idea that a single platform is going to replace mutation-specific tests is currently no more than a hypothesis, Robson said. "A lot of people are deeply invested in this idea," he said, "but whether or not it's actually going to turn out to be the case remains to be seen."

Pfeifer said he was unsure about when the science is proven in the context of follow-on drugs. A drug can be shown to be safe and effective in a specific patient population, but that is not the complete answer—it is just what is known at the moment, he said, and people tend to overgeneralize what they know, as they do with tests. When tests are first approved, they appear to be solid, but over time, as more is learned about the test and the disease associated with the test, it becomes clear that the test is not necessarily optimized with regards to patient groups and precise threshold levels. The question then becomes how to incorporate new information into the formulation and use of the test, he said.

Pfeifer agreed that NGS could be the "ultimate companion diagnostic." But three issues are important to consider, he said: which technical procedure to use, how to improve the reproducibility of bioinformatics analyses with the same dataset, and which type of regulatory environment would support linking data analysis with patient outcomes. Pfeifer added that the same information can be fed into two different bioinformatics systems and produce two different answers. "That should be profoundly concerning to anybody who is proposing the clinical utilization of next-generation sequencing," he said.

Robson pointed out that next-generation sequencing has different applications in the sense that it can be used to produce different amounts and types of information. Degrees of sequence depth, the number of genes, the extent of the genome and, in oncology, whether germline or somatic mutations are covered all raise issues relating to the complexities of interpretation and incidental findings. "It's important to maintain an awareness of those subtleties," Robson said.

Nevertheless, Robson added that his institution is already using next-generation sequencing in cases where potential germline predispositions are difficult to define phenotypically. For instance, he said, "pediatric bone marrow failure syndromes can be due to a number of different things that are hard to sort out phenotypically and are very expensive to test serially." As a result, Memorial Sloan Kettering uses next-generation sequencing panels to gather as much information as possible for conditioning regimens prior to transplantation. It also uses this technology with some cancer susceptibility syndromes that are difficult to sort out, such as oligopolyposis in the colon, which can be caused by mutations in any of a number of genes. "Again, if you do it serially, it gets pretty expensive pretty fast," Robson said. "So a multiplex panel is actually less costly and faster."

With a previously unidentified mutation, it may be possible to predict the functional consequences using a generic paradigm that takes into account whether the mutation causes premature termination, abnormal splicing, or another functional effect, Robson said. In that case, a generic paradigm can be applied with a relatively high degree of confidence. Methodologies are already available that assign levels of confidence that a particular variation is likely to be deleterious and functionally significant, but in other cases, such as determining the importance of a missense mutation in the non-kinase domains of PI3-kinase, this approach will not work as well. "From a regulatory standpoint," Robson asked, "what confidence annotation do you require before that [information] becomes part of the label?" He added that oophorectomies are performed based on *BRCA1* mutations that are "probably pathogenic, but not necessarily definitely pathogenic."

Frueh said that next-generation sequencing will generate a huge amount of information which can then inform the decisions made by physicians and

patients. But he also noted that other forms of information are also available, such as epigenetic information and data about the microbiome. When, he asked, do physicians and patients become responsible for deciding how much and what types of information they want?

Cost of Sequencing

Pfeifer pointed to the existence of a "crossover point for health care financing." Next-generation sequencing will soon provide information that is "irresistible" to have because it will contain more information about the disease. Payments will move increasingly to a bundled model that will provide a set amount of money for diagnosis and treatment. Health care networks will then be able to decide how to spend that money, and it will force health care systems to prioritize what they are doing. The question then will be whether a test, used as indicated or in an off-label way, can provide useful information that is not otherwise available.

Wylie Burke, professor and chair, Department of Bioethics and Humanities, University of Washington, said that while genomic technology could improve quality of care and reduce costs, it also has the potential to drive costs upward because there is a temptation to acquire as much data as possible. Burke noted that the health care system cannot afford to pay for all of the research that needs to be done to determine the utility of genomic information. "That's not health care—or at least at a certain point it's not health care," she said, "because it's not evidence-based interventions to improve outcomes. It's learning in the hope that we may improve outcomes in the future." Terry also pointed to the potential for genomics to generate disparities in health care because some patients may have better access to information or to providers and may know how to navigate the system to gain the information that they need.

Pfeifer explained several other ways in which genomics can add costs. Clinicians may order complex genomic tests in patients who are not well enough to benefit from the results. Or a test may suggest but not guarantee that a costly treatment will be effective. "Some of these cases we have seen are homeruns, but the reality is that not everything is," he said. Sometimes a test indicates that a patient will not benefit from a treatment, but a provider will use that treatment anyway. While some are willing to add costs to acquire more information, Pfeifer said, there is a reluctance to use the information for inaction.

DIRECT-TO-CONSUMER TESTING

The use of genetic tests directly by consumers for the detection of germline mutations presents a number of issues concerning consumer choice,

innovation, ethics, and education. Terry said that the direct-to-consumer route is important because patients need to have some sort of relationship with the system and need to be able to make sure that their information and data are being used properly. Robson emphasized that the quality of the information and education provided to consumers along with their genetic test results for inherited mutations are important. Having access to genetic results enables patients to be at the table when value conversations are happening, Terry said.

Direct-to-consumer genetic testing is an experiment that is pushing the envelope, Terry said. Projects like the Personal Genome Project are careful about saying what has been validated and what has not been, but many questions need to be resolved, such as who owns a person's genome sequence, where it will be stored, and how it will be distributed. Old models to address these questions are not necessarily going to work, Terry said.

Finally, Pfeifer agreed with Terry that everyone is a consumer of health care and they are involved in different areas along the spectrum of the health care system. As taxpayers, people want investments that are effective and provide value. As consumers of health care, they want tests and treatments that are safe and effective. "We're all in this together," Pfeifer said. "We are just at different points of the spectrum."

4

Perspectives of Diagnostic Test and Pharmaceutical Developers

Important Points Highlighted by Individual Speakers

- There are many sources of IVD performance error—from patient samples to data interpretation and reporting—and establishing clinical validity is just as important as establishing analytical validity for assuring that patients receive the correct therapy.
- Using robust scientific evidence for determining if benefits outweigh the risks for using a companion diagnostic should be the basis for creating a level playing field for regulating IVDs and LDTs.
- The implementation of a strong external quality assurance program for IVDs and LDTs is needed as a standard for validating biomarker measurements across laboratories.
- Studying patients who tested negative for a biomarker but who could have benefited from the associated therapy is important for optimizing patient populations for drugs and for understanding disease biology.
- Development of test registries to compare test results across multiple laboratory settings could establish stronger links between test performance and clinical outcomes.
- Several pharmaceutical companies have established internal diagnostic groups for co-development, but the companies have not overlooked the value of collaborating externally with experts.

To assess the present and future prospects for the use of co-developed companion diagnostics in drug use and development, speakers representing groups involved with test development as well as speakers representing pharmaceutical manufacturing were invited to share their perspectives. A theme that emerged was the importance of obtaining analytical validity, clinical validity, and clinical utility evidence for tests, regardless of how the tests are specifically developed, distributed, or conducted.

DEVELOPING THE EVIDENCE FOR VALIDITY AND UTILITY

A number of important shortcomings currently affect clinicians' use of IVDs. One important issue is that IVDs vary in performance and have many sources of potential error, said Walter Koch, vice president of global research at Roche Molecular Systems. No fewer than a dozen different methods are currently used for mutation detection, he said. Furthermore, tumors are heterogeneous, which raises the possibility that variability in tissue sampling may lead to results based on just a few cells that may not accurately reflect the cellular makeup of the tumor. In addition, reagents used in tests can be variable because of considerable lot-to-lot variation, and in manual analyses data interpretations may vary. Koch noted that two studies performed in Europe support the notion that procedural steps are not well controlled in some laboratories. In fact, for *KRAS* testing, only 70 percent of the laboratories accurately reported all of the mutations (Beau-Faller et al., 2011; Bellon et al., 2011; Dequeker et al., 2011).

In addition to the *KRAS* example above, Koch cited an example from Roche's clinical trials for Zelboraf, where the cobas® 4800 BRAF V600 Mutation Test was used to identify patients with melanoma tumors harboring the V600E BRAF mutation (Cheng et al., 2012). While Koch noted that FDA recognizes Sanger sequencing as the "gold standard" for variant detection in the absence of an FDA-approved test, he pointed out that it may be poorly suited for cancer tissue mutation analysis because of known poor sensitivity for samples containing less than 25 percent mutant alleles, which is frequently the case in cancer (Anderson et al., 2012; Halait et al., 2012). Other potential consequences of relying on Sanger sequencing include invalid results (no results), false negatives (incorrectly identified as wild-type), and false positives (incorrectly identified as BRAF V600E) that may occur more often, as reported by Anderson et al. (2012). The downstream clinical implications of these errors could include inappropriate denial or delayed access to Zelboraf or patients inappropriately receiving the drug, which may lead to preventable toxicity in addition to poor efficacy. "Today, a lot of laboratories are using [Sanger] technology to do these kinds of mutation analyses," Koch said. "They are perhaps inappropriate for this use."

Even tests using the same technology can produce discrepant results (Gonzalez de Castro et al., 2012). A comparison of the cobas® 4800 BRAF V600 Mutation Test with Therascreen (Qiagen) BRAF RGQ found that the two methods produced different results in tumors with necrosis and low tumor cell content (Longshore et al., 2012). As a result, some patients would be assigned to the wrong category for receiving or not receiving the drug, Koch said.

Response to Potential Solutions

Several suggested stakeholder solutions were proposed to address the current co-development pathway (see Box 1-2), including an American Clinical Laboratory Association proposal that clinical validity should be assured for laboratory tests. Koch examined the standards for clinical validity in the proposed federal legislation, Modernizing Laboratory Test Standards for Patients Act of 2011 (H.R. 3207), which states, "One or more studies published in a peer-reviewed journal that is generally recognized to be of national scope and reputation, or data from unpublished studies conducted by the submitter or for which the submitter has obtained a right of reference, shall be sufficient to constitute reasonable assurance of the clinical validity of the claimed uses." Koch then suggested that this may not be sufficient to decide on routine use of biomarker testing; rather, replicated studies and more substantial clinical validation should be required.

The proposals made by AdvaMed as well as by FDA reflect a risk-based approach, Koch said. He thought that this solution could be improved upon by answering questions about regulating tests when there is already an existing test and about whether an alternate Class III equivalence mechanism could be used because repeating a clinical trial is not practical. "All in vitro diagnostics, regardless of where they are made—by a manufacturer or a lab—should be subjected to similar regulatory approaches," Koch said. "At the end of the day, the same risk–benefit profiles apply to patients when a therapeutic decision is based on that result. So why should they be treated differently?"

Koch disagreed with the recommendations from CAP that "companion analytes" should be defined, because IVDs clearly vary in both analytical and clinical performance. He also disagreed that a single diagnostic prevents further research, as suggested by the American Society of Clinical Oncology (ASCO). "Our own drug company—and the academics that I work with—continue to dig into the complex biology of cancer," he said. "They are not limited simply by that companion diagnostic."

Koch said that payment reform is needed "to recognize the value of advanced medical diagnostic tests, their impact on health care, and the resources needed to develop and clinically validate them." Inadequate pay-

ment systems seem to hinder innovation as well as patient access to new tests; however, Koch said, a potential alternative strategy has been suggested by Medicare's Molecular Diagnostics Services Program at Palmetto GBA,[1] which issues reimbursement based on an assessment of levels of analytical and clinical evidence.

LEVELING THE PLAYING FIELD

The co-development process has several benefits, said Pamela Swatkowski, director of regulatory affairs for Abbott Molecular. It provides an opportunity to evaluate the drug and the device in one trial and to select an optimum patient population for a smaller clinical trial. For the pharmaceutical manufacturer, an effective marker can improve the effects of the drug. However, a pharmaceutical company needs to know whether the performance of a diagnostic is robust and sometimes LDTs may not give that same level of assurance that the correct population has been selected. For diagnostic manufacturers, an effective marker can facilitate use by pharmaceutical manufacturers as well as by clinicians. For example, Swatkowski said, co-development enables new types of diagnostic claims, and patients can be well characterized and receive extensive follow-up and monitoring of outcomes.

A level playing field is needed for all tests to determine device safety and efficacy by answering the basic question of whether "there is enough valid scientific evidence that the benefits outweigh any probable risks," Swatkowski said. She agreed with ASCO's point about the challenge of regulatory uncertainty regarding FDA oversight of companion diagnostic LDTs. Having a better understanding of the enforcement discretion of LDTs would be useful for providing evidence for clinical utility and not just analytical performance.

After the test was approved by FDA in 2011, Koch observed that other labs were advertising BRAF tests for Zelboraf use within a short period of time. However, it was not evident what the performance characteristics of their tests were, what technologies were being used, or how the test might relate to the FDA-approved test. To Koch, the situation was similar to a drug being approved and having a generic drug available soon after for the same application. In this circumstance "it just doesn't seem like a level playing field," he said.

Swatkowski encouraged FDA to work with industry "to define those requirements for development of subsequent assays after the first com-

[1]Palmetto GBA. Homepage. See http://www.palmettogba.com/palmetto/palmetto.nsf/SiteHome?ReadForm (accessed October 10, 2013).

panion diagnostic is approved, since we all know that samples from the original trial won't be available."

Response to Proposed Solutions

With respect to various stakeholder proposals (see Chapter 1 and Box 1-2), Swatkowski highlighted the proposal made by the Coalition for 21st Century Medicine that developers of tests, whether IVDs or LDTs, "need to offer proof of clinical validity in order to obtain coverage and reimbursement," with "reimbursement based on the performance of the test and the evidence that supports that performance." Pfeifer's interpretation of the proposal by the Coalition for 21st Century Medicine is that coverage and reimbursement should be based on performance of each technique. The assumption that a companion diagnostic at some level will provide a level of performance that cannot be matched by LDTs will probably not be borne out, Pfeifer said.

Swatkowski also agreed with the position of AdvaMed that tests should be regulated according to risk, despite the challenges of doing so. For instance, though the CAP proposal emphasizes the analyte be used for drug efficacy, defining an analyte this way does not address the test technology and assay variability among different methodologies. An important point to make, she said, is that an IVD is a system that extends from sample preparation through test generation and bioinformatics to the "algorithms that determine whether a patient is positive or negative, and the cutoff that's used is really the heart of the IVD device."

AREAS FOR CONSIDERATION

Additional considerations, including financial reimbursement and coding requirements, may need to be addressed in order to improve the current system of IVD use. Swatkowski highlighted several issues related to reimbursement for IVDs, including the need for transparent coding, especially in preparation for next-generation sequencing. With the current coding system, payers do not necessarily know what they are paying for, Swatkowski said. For example, the test for a particular analyte may not be transparent as to whether the test has been FDA-approved or is an LDT. In addition, differential payments should be considered for clinically validated FDA-approved assays, she said, as is currently done with innovative drugs.

FDA should also consider outlining the requirements for adding additional (i.e., second and third) therapies to the IVD device labeling, Swatkowski said. While the complete dataset from the original clinical trial may not be required, additional statistical testing would be useful to calculate the negative and positive predictive values. Using medical infor-

mation from consenting patients may be a way to accomplish this so that the demographics of the patient population would be equivalent to those used in the original clinical trial, Swatkowski said. She highlighted several development issues for FDA to consider, including continued joint meetings that include the relevant parts of FDA, pharmaceutical sponsors, and IVD device sponsors.

NGS will forcibly change the current landscape of diagnostic testing, Swatkowski said. It will be necessary "to understand how we can analytically validate data that's generated by these platforms that are equivalent to already cleared or approved" tests based on similar but different technologies that have been cleared or approved. The goal will be to use the analytical data to connect the information to already generated outcome data for clinical utility, Swatkowski said. An important issue for whole genome sequencing will be the selection of suitable reference human genomes for validation purposes. For example, extensive information technology and data storage capabilities to fully analyze complex datasets will be needed, Swatkowski said. Because there are a variety of platforms and sequencing technologies, "any regulatory requirement should have the flexibility to adapt to rapidly changing technology."

CONSIDERATIONS FOR IVDs AND LDTs

The single aim of Amgen's companion diagnostics effort is to "accurately identify those patients who can benefit most from therapy," said Scott Patterson, executive director of medical sciences for Amgen. "Patients who cannot benefit from a particular therapy should not be getting the drug."

Patterson outlined several implications for this objective. First, he said, false positives or false negatives should be limited, depending on whether the biomarker makes a positive or negative determination. In other words, the "robustness" of a test is critical. Second, the test must be available in all markets where the therapy will be commercialized and not just within the United States. Third, diagnostic tests should not be used as a means of restricting access to therapeutics. Finally, as others have mentioned during the workshop, efficient testing of multiple biomarkers should be done early in the course of treatment, Patterson said.

Because FDA approval of an IVD provides the desired level of confidence for robustness in a test, Patterson said, if another assay is going to be used, it should meet the same level of evidence. Given the possibility that not all tests for a certain biomarker are equal, then determining a patient's eligibility for a drug by an analyte is only supported if rigorous concordance is established with an IVD that has associated clinical utility. If such an IVD does not exist, then a rigorous analytical concordance equivalent to the appropriate elements of premarket approval validation should be required,

Patterson said. Also, if no IVD exists, commutable standards to validate biomarker measurements across individual laboratories are needed. Lastly, ongoing and challenging proficiency testing and external quality assurance (EQA) programs are critical to ensure standards are maintained, whether for approved IVDs or LDTs. LDTs will not go away, he said, but standards need to be high across all laboratories.

Physicians and patients should be educated in order to increase understanding about the quality and status of the test being offered. At the same time, more robust EQA programs are needed in order to produce consistent patient selection along with transparency of results from EQA laboratories (van Krieken et al., 2013). Additionally, Patterson said, there should be an investigation into the utility of testing earlier in the course of treatment for multiple biomarkers, both for conserving samples and for addressing payers' concerns.

A "test needs the ability to discriminate at a clinical decision point," Patterson said, with the decision point serving as a cutoff point for identifying and classifying patients. Furthermore, there should be a biological understanding of the biomarker and the cutoff if multiple therapies are to be addressed using the same biomarker. "We really want to try our best to understand the biology behind that biomarker, such that if a cutoff is determined, it will, therefore, be applicable to other therapies in that class," Patterson said.

In the case of binary test results (i.e., somatic mutation tests), data suggest that greater sensitivity is better because an assay does not provide a yes/no answer, and this is where the cutoff is important, Patterson said. However, variation in the ability of a laboratory to identify mutations, caused by different levels of test sensitivity, may pose a risk to patients. "Again, it gets back to really having rigorous performance characteristics established for the tests, wherever those tests are being conducted," Patterson said.

Other assays, such as transcript or FISH assays with continuous variable results, face different variability challenges. The percent of cells expressing the biomarker and the level of biomarker expression can vary within a sample. As with binary tests, biological plausibility is needed to support the cutoff that was established in the clinical trial outcome data. Even binary tests are unlikely to always identify the same patients, Patterson said, and "continuously variable tests pose greater issues."

Regarding the individual proposal for financial reimbursement (see Box 1-2), Patterson said that, in principle, a test could be reimbursed along with a drug, but the challenge will come in implementing such an approach. "Will it also stop tests for which the performance characteristics are not as well determined as the IVD being used? Or will all such tests be reimbursed even if their performance characteristics are unknown?" When testing is conducted by a single or limited number of laboratories,

the barriers to reimbursement for the test along with a drug appear to be fewer—a fact that may be related to the consistency of results and transparency regarding methodology, said Patterson. Ultimately, the reimbursement logistics associated with distributed testing would need to be taken into account.

If the goal of the combined cost model (see Box 1-2, individual participant submission) for the drug and test is to enforce the use of IVDs, a laboratory is unlikely to use an LDT because it would be paid only a service fee, said Bruce Quinn, senior health policy specialist with Foley Hoag LLP (see Figure 4-1). But payers could not institute such a system unilaterally because that would require that the test be provided for free to the laboratory by the pharmaceutical company or the test manufacturer. The payer and laboratory could work together to provide the LDT, but they would be at a substantial financial disadvantage in doing so, and this would also risk having the laboratory or the pharmaceutical company give free tests to a hospital system in return for using its drug, which would raise potential conflict of interest issues.

Combining payments for tests with payments for therapeutics is an interesting idea, Pfeifer said. In a world of bundled payments, a health care organization may be given a certain amount of money to take care of a patient with cancer. If so, decisions about how to use that money may occur at the local rather than national level. "Each individual institution may have to decide" how to use the allotment, he said.

The combined cost model may not be viable after generic versions of a drug become available and the overhead no longer exists to provide free test kits, especially if the test has to be provided to a large number of patients to find just a few who will benefit from a treatment, said Quinn. There are other ways to enforce the use of an IVD. For example, in theory, LDTs could be made illegal, or the coding of the test could be reformed to make it clear that an IVD was used. "You can't [change the coding] today, but that could be constructed in a few months in the coding system," he said.

Enforcing an IVD monopoly would enable a manufacturer to raise the price of a test, leaving pharmaceutical companies and payers without an alternative. This approach does not resolve the challenges of limited tissue specimens and provides no incentives for competition or improved products. However, Quinn said, a more robust CLIA does not resolve return on investment problems for the IVD manufacturers who go through FDA and then find that their approval is followed by the production of similar LDTs.

TEST PERFORMANCE IN USE

Once a co-developed drug and a companion diagnostic are approved by FDA, "what are the ramifications as that drug is used in the marketplace?"

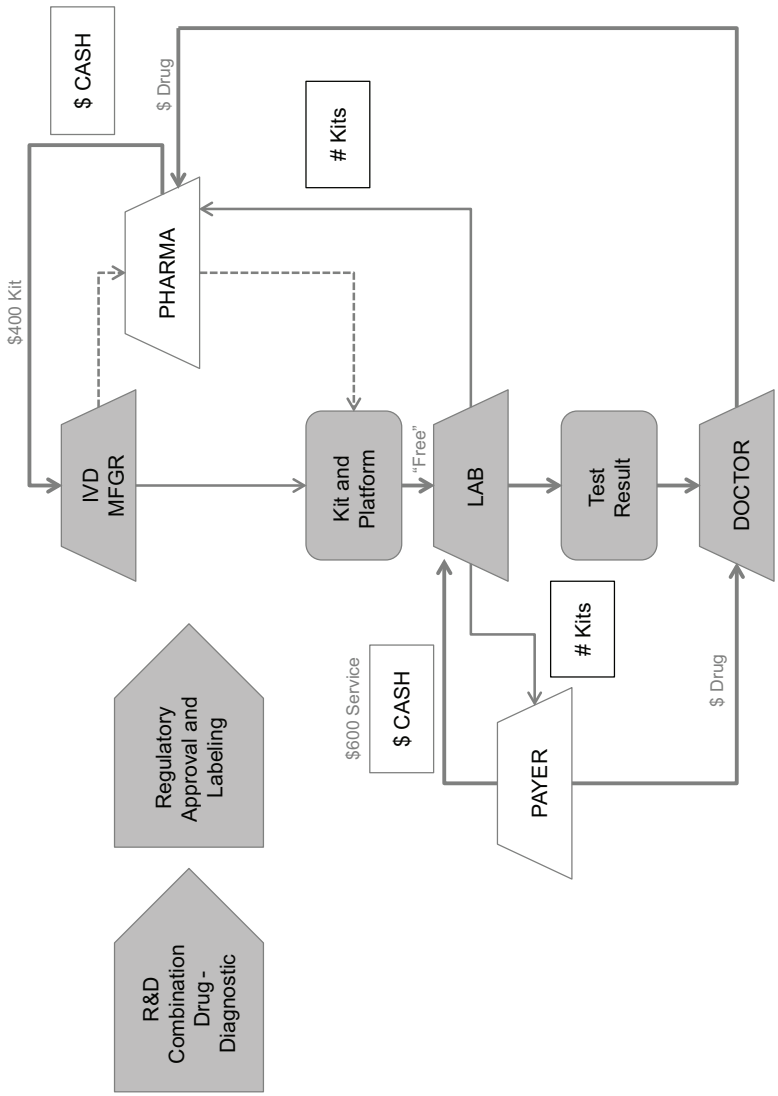

FIGURE 4-1 Proposed payment model for connecting the costs of co-developed companion diagnostics to those of the related drug.
NOTE: IVD, in vitro diagnostic; MFGR, manufacturer; PHARMA, pharmaceutical company; R&D, research and development.
SOURCE: Quinn, IOM workshop presentation on February 27, 2013.

asked Richard Buller, vice president and head of oncology clinical development at Pfizer. Will clinicians use only the FDA-approved test, or will other LDTs be used preferentially? Demonstrating clinical benefits should be the gold standard for a test, and in that way clinical validity for tests used should be ensured, Buller emphasized.

A test can have either a positive result or a negative result, and a patient can either benefit or not benefit from a drug, Buller said. When a positive test result leads to positive results from the use of a drug, then the patient was correctly selected for treatment. When a negative result points toward a lack of benefit, it is generally the case that a decision will be made to not treat a patient. What about the false positives, Buller asked, where there is a positive test result but the use of the drug does not lead to clinical benefit? These patients may turn out to be as non-responders, or technical issues may have affected the assay or biological sample. These cases of false positives provide an opportunity to understand the biology of the disease. Resistance mutations may have developed during the course of the treatment, or the resistance mutations may have been present originally, in which case those patients may show no improvement and need a different drug, Buller said. He explained that the "reference standard" needs to be a clinical outcome or clinical utility for companion diagnostic development.

With false negatives, it is possible that a patient could have benefitted from the use of a drug despite the difficulties with identification, Buller said, but marker-negative patients need to be tested at some point in the development process to determine if the therapy is of benefit to them. The magnitude of the problem of false negatives increases with the decreasing prevalence of a disease; when only a small percentage of patients have a marker, a test with a large percentage of false negatives—i.e., that misses many patients with the marker—would have a major impact. Ultimately the identification of false negatives may create opportunities to more fully understand disease biology.

The performance of tests can vary greatly, even after approval. Buller exhibited the positive rate of the Abbott Vysis LSI Break Apart FISH Probe Kit which was used to test for *ALK* in four different central laboratories following FDA approval of the test and drug. The positive test rates ranged from 2.1 percent to 5.5 percent, Buller said. "There are probably some laboratory testing issues there" that were related to the screening approach and not the assay performance.

Pfizer has a commitment to do post-market evaluation of test-negative patients, Buller said. It also has been supporting method comparison studies across sequential cases, multiple platforms, and multiple countries to see how different tests perform. Pfizer is currently working with Ventana Medical Systems, Inc., to submit a second ALK test to the premarket approval process, and it is working with other central laboratories to understand

testing outcomes in the marketplace. In particular, it is looking at patients who have discordant test results in order to improve understanding of the disease biology along with differences in testing.

TEST REGISTRIES

The use of registries as a test bed for comparative effectiveness research across the spectrum of different diagnostic testing platforms was debated during the ensuing panel discussion. The moderator of the session, Geoffrey Ginsburg, director of the Center for Genomic Medicine at Duke University, specifically queried the four speakers about the potential value of test registries for comparing the efficiency of multiple LDTs.

Buller observed that not just payers but also diagnostic manufacturers and pharmaceutical companies would be interested in a registry because test results and drug use could be linked to test performance and clinical outcomes. Swatkowski noted that a registry could collect information on multiple tests, but in that case it would still be necessary to know the details of the tests in order to make comparisons, such as the technology employed and the cutoffs used. This may present a bioinformatics challenge, she said, noting that "we would have to plan the variables that would be collected in order to make that registry useful."

Patterson said that a registry is an interesting idea that could reveal how well laboratories are performing tests. A "robust and challenging EQA program" would be another way to achieve that end, he said. Buller suggested that starting with the larger high-volume laboratories would be a good way to see if the approach was useful.

IN-HOUSE DIAGNOSTIC UNITS

Ginsburg also asked whether pharmaceutical companies are setting up diagnostic units to develop companion tests internally rather than relying on outside companies. Patterson said that Amgen has decided not to take that approach, because the company works with expert diagnostic companies that can develop the whole range of biomarkers that it needs. "We work on a very broad range of analytes," he said, "and to cover all those even in one company is very difficult." However, Amgen does have a department of molecular science that works on biomarker research in early phase trials.

A workshop participant said that Novartis also has an integrated companion diagnostic group.[2] In this way, the company could have access to

[2]Novartis: Our Global Capabilities. See http://www.novartisoncology.com/about-us/our-global-capabilities.jsp (accessed October 10, 2013).

internal expertise on all aspects of IVD development and ensure an integrated approach to co-development. But Novartis also continues to work with external partners, depending on the needs of the individual therapeutic being developed.

Buller said that Pfizer has an integrated group specializing in the diagnostic aspect of co-development, but it chose not to bring a specific technology into the company or to buy a diagnostic company because of the rate at which technology is changing. Koch said that Roche has both a standalone diagnostics business and a therapeutics business. While its pharmaceutical partners, such as Genentech, do have integrated diagnostics groups, they primarily focus on understanding disease biology both in preclinical and early clinical trials. Buller and Koch both noted that by not having internal diagnostic units, the enterprise has more flexibility to collaborate with the best external groups.

5

Perspectives of Payers and Regulators

Important Points Highlighted by Individual Speakers

- The regulation of diagnostic medical devices should be performed by FDA, which should use a risk-based approach.
- IVDs and LDTs that claim equivalence should be subject to the same regulatory scrutiny.
- A decision should be made between either an FDA-based or a CLIA-based pathway to market.
- Payers' concerns center not on a diagnostics path to market, but rather on whether the test is safe, clinically effective, and cost-effective.
- Next-generation sequencing presents a challenge for making payment decisions because collecting extra information is not traditionally covered unless it is shown to be safe and useful, regardless of any potential cost savings.

Several regulators, legal consultants, and payers present at the workshop, offered unique perspectives on how co-developed companion diagnostics should be regulated—exclusively by FDA or exclusively through CLIA or via a combined approach in which FDA determines which tests need further review and which can enter the market under CLIA. Private payers who are responsible for reimbursing the costs of diagnostics are not concerned with the specific pathway used in regulation; instead they

are concerned with whether a test has clinical utility, is innovative, and is cost-effective.

ALLOW THE CURRENT SYSTEM TO WORK

In the current co-development pathway, different stakeholder groups gather different types of evidence. CLIA assures analytical validity and the quality of tests performed in accredited laboratories in the United States, and this regulation is broad in scope, said Steven Gutman, strategic advisor for Myraqa, Inc. FDA, on the other hand, assesses analytical and clinical validity for commercially distributed IVD kits. Gutman argued that a unique aspect of FDA as a regulatory authority is that it performs an in-depth, hands-on review of tests. The challenge with the current regulatory system, Gutman said, is that "FDA does not currently provide [this type of review] for laboratory-developed tests." In the current regulatory environment, it is the third-party payers, the practitioners of evidence-based medicine, or the guideline developers that are evaluating the clinical utility of tests, but, Gutman said, "this work is unfortunately non-standardized, non-coordinated, and is performed with variable transparency."

As a starting point for the regulatory oversight of companion diagnostics, Gutman provided what he called a "modest proposal"—that FDA, CLIA, and third-party payers should be allowed to "do their jobs." CLIA should regulate laboratories to "assure a quality operation and to allow for a sampling of evidence that analytically valid systems are in place," but CLIA should not be expected to regulate medical devices pre- or post-market because the Centers for Medicare & Medicaid Services (CMS) lacks the authority, experience, and resources for this additional regulation. FDA should continue to regulate diagnostic medical devices, and this regulation should be risk-based. The role of third-party payers is to make evidence-based decisions, and "cost containment, cost-effectiveness, and cost consciousness" should all be issues for discussion because of the significant cost of health care, Gutman said.

The conversation around regulation should be focused on evidence-based medicine, but to accomplish this, solid data is required to "get the science right," Gutman said. Stakeholders should recognize the "four Rs," he said: the right drug, the right patient, the right time, and the right data or information. "We need leadership in the design and orchestration of studies—something that . . . would aid the FDA, third-party payers, and maybe even CMS," he concluded.

EVALUATING TWO SYSTEMS

As companion diagnostic products, LDTs *are* IVDs, but there are two very different regulatory mechanisms (CLIA and FDA, respectively) that

apply to them, and "they both can't be right," said Bradley Thompson, a member of the firm Epstein Becker & Green and a general counsel to the Combination Products Coalition. The goal, he said, is finding an optimal regulatory system to balance the innovation and the safety of the tests and to determine which regulatory mechanism does the best job of managing that risk. The two regulatory pathways have many differences, including how the tests are reviewed for quality during manufacturing, said Thompson (see Table 5-1). The premarket approval process for high-risk products requires extensive involvement by FDA before the project reaches the market, an exacting quality system for manufacturing, adverse event reporting, and establishment of clinical validity before the test is used, none of which is required under the CLIA process. If two products are the same, he asked, then why should they not be regulated the same way?

The main problem of having FDA review both IVDs and LDTs, as proposed by AdvaMed (see Table 5-2), is that there are insufficient resources for this approach, Thompson said. The way to solve this issue would be to have FDA focus on the high-risk tests, and the low-risk products can go

TABLE 5-1 A Perspective on Current Requirements for IVDs and LDTs

Requirements	IVDs (held to FDA standards)	LDTs (held to CLIA standards)
Premarket review and approval for tests	Yes, for higher risk tests	No
Manufacturing tests under a quality system, e.g., • Design controls • Process controls • Complaint handling	Yes	No
Reporting adverse events	Yes	No
Annual reports	Yes, for higher risk tests	No
Establishing clinical validity before using test	Yes	No[a]
Establishing clinical utility before using tests	Yes, as needed	No
Regulation of test performance claims	Higher standards (FDA and FTC requirements)	Lower standards (FTC only)

NOTE: CLIA, Clinical Laboratory Improvement Amendments; FDA, Food and Drug Administration; FTC, Federal Trade Commission; IVD, in vitro diagnostic; LDT, laboratory-developed test.

[a]Laboratory directors must assure tests are of sufficient quality for use in patient care, but there is no evaluation of clinical validity along the lines required by FDA.

SOURCE: Thompson, IOM workshop presentation on February 27, 2013.

TABLE 5-2 A Perspective on Possible Solutions from AdvaMed and ACLA

Requirements	AdvaMed[a]	ACLA
Equal treatment of LDTs and IVDs under review	Yes	No (LDTs remain subject to less regulation)
Premarket review/ Approval for tests	Yes, for higher risk tests	No
Manufacturing tests under a quality system	Yes	No
Establishing clinical utility before using tests	Yes, as needed	No
Establishing clinical validity before using tests	Yes	No[b]
Annual reports	Yes, for higher risk tests	No
Reporting adverse events	Yes (deaths, serious injuries, and malfunctions)	Limited (deaths and serious injuries only)
Regulation of test performance claims	Higher standards (FDA and FTC requirements)	Lower standards (FTC and disclosing test limits)

NOTE: ACLA, American Clinical Laboratory Association; CLIA, Clinical Laboratory Improvement Amendments; FDA, Food and Drug Administration; FTC, Federal Trade Commission; IVD, in vitro diagnostic; LDT, laboratory-developed test.

[a]Leverages existing information to reduce premarket regulatory burdens.

[b]Some clinical utility data are collected, but not subject to agency review before the test is used.

SOURCE: Thompson, IOM workshop presentation on February 27, 2013.

to market without review, he said. This approach would "leverage existing science to reduce premarket FDA regulatory requirements based on risk and familiarity with the technologies and the science," Thompson said. With higher risk would come greater requirements, so it would be likely that companion diagnostic tests would be subject to the highest regulatory standards because of the risk and the novelty of the tests.

Strengthening CLIA, as proposed by ACLA, would require premarket notifications, including clinical validity information, so that laboratories could use tests immediately following the submission of these notifications, Thompson said. If clinical validity evidence is not available and there is an immediate health risk, CMS could then prohibit the use of a test. This proposal would require adverse event investigation and reporting, and this and other information would be stored in a test registry. The enhancements proposed by ACLA would not address many of the differences between the two systems, Thompson observed. In particular, they would not require a premarket review or a quality system for manufacturing, he said.

Thompson proposed that FDA be the body in charge of regulation

because FDA adds value in the process of regulating products. FDA staff has extensive experience with reviewing products, and they know the types of problems that can arise and can often anticipate areas of concern and bring a fresh perspective for identifying ideas that the sponsor may not have thought of. At the same time, substantially more guidance is needed from FDA to make the development of companion diagnostics more efficient and to promote innovation. Manufacturers need to work extensively with FDA on a case-by-case basis to answer these questions so they can determine what is needed scientifically to support safety and effectiveness.

The current system need to be reformed, Thompson concluded. Whatever system is adopted should apply equally to both IVD manufacturers and laboratories, commensurate with risk. If regulation through a strengthened CLIA is enough to assure the safety and effectiveness of companion diagnostics, there is no reason for FDA to regulate diagnostics too, said Thompson. If laboratories can independently, under CLIA, do everything needed to ensure the safety and effectiveness of a product and they do not need approval to purchase reagents from an FDA-approved source, then why, he asked, would FDA need to be involved?

However, Debra Leonard, workshop co-chair and, at the time of the workshop, professor and vice chair for laboratory medicine at Weill Cornell Medical Center of Cornell University, said that the distribution, use, and payment models that govern IVD companies and clinical laboratories are different, and therefore they need different regulatory environments. A more robust CLIA is needed to bring the existing CLIA up to date, she said, but there is a role for FDA in regulating products that will be sold by companies.

Pfeifer contended that an artificial similarity between the two pathways was created when choosing one over the other was proposed by Thompson. FDA approval is needed for drugs to ensure that the patients with a specific mutation are an appropriate group to treat with that drug, while optimizing a test to detect the mutation is a fundamentally different endeavor, Pfeifer said. Establishing safety and efficacy with FDA and determining the sensitivity and the specificity of the laboratory test are different issues. "I would argue that you need both" regulatory systems, Pfeifer said. Once an FDA-approved companion diagnostic becomes available, CLIA could regulate the test metrics for follow-on tests in the certified labs, Pfeifer said.

TEST PRICING

Joanne Armstrong, senior medical director and head of women's health at Aetna, said that the outcome achieved is more important than the regulatory pathway used to bring a co-developed companion diagnostic test to market. While noting that each regulatory process has particular strengths—FDA's assurance of effectiveness and CLIA's flexibility and

allowance for innovation—overall, the important factors for management of medical costs are how good these products are and whether they improve outcomes, avoid harms, and reduce costs.

With rising health care costs in the United States, it is projected that health care spending will be almost 20 percent of the gross domestic product by 2022 (CMS, 2013). Costs of health care premiums are rising as well, and over the past decade, these costs have been shared equally between patients and their employers, Armstrong said. As a result, consumers have become increasingly responsible for more of the costs of health care and, thus, responsible for the costs of innovation and technology. These advancements in technology "must be valuable" to patients, Armstrong said, because they are bearing much of the costs.

Managing medical costs while optimizing value is important; as a country, we are currently spending much more on health care costs than we can currently afford. "We need to make sure that the products that are put out there and that are promoted actually can reduce total costs in the real world," Armstrong said. Reducing costs can occur by a sequester approach or through determining what adds value, and the latter concept means that science needs to be effectively translated into the clinic.

The costs of genetic tests are still relatively modest, but they are growing rapidly—at about 11 percent per year, according to Armstrong. Still, the major focus of attention at insurance companies is obesity and heart disease, and it is a challenge to devote time to discussing reimbursement about other public health issues that may be of lesser priority. Aetna, for example, spends less than 1 percent of its total medical costs on diagnostics, Armstrong said. For Aetna to reimburse for diagnostic tests, they "look for analytical validity, clinical validity, and clinical utility," and many of the tests have limited information on clinical utility.

Payers look for three things in deciding which co-developed tests to support, Armstrong said. They look for effective technology, innovation, and cost-effectiveness. Effective technology requires knowing that a test is analytically and clinically valid and that it has clinical utility (Quinn, 2010). The transparency of test performance data is needed because these data are important for determining effectiveness. Today, no organization "owns" technology assessment. "We do it, but there's really not an independent body that does it," she said. "We would welcome a trusted independent source of technology assessment, especially for high-risk tests." Innovation and adapting to change also are important, she said, because "new technology platforms drive not just clinical improvements, but clinical efficiency," and next-generation sequencing may be an example of this.

Value-Based Pricing

Lowering health care costs through value-based pricing models should create incentives for important and useful diagnostics to come to the market, Quinn said. The challenge, Armstrong said, is that the business model does not support new development because once labs produce innovative and less expensive products, this leads to decreased revenues. "Combination diagnostics are actually easier to value because there is one drug and one outcome," Quinn said. The Oncotype DX® test is an example of this, and it was close to revenue neutral overall, he said. Most other diagnostics are more complicated because they have many uses beyond just the question of whether to administer chemotherapy. Positron emission tomography scans, for example, have many different uses and purposes that vary from patient to patient, Quinn said.

Aetna would support the development of reimbursement models that reward improvements in outcomes in real-world settings, Armstrong said, but this approach can be difficult. Paying for value also implies not paying for things that the data indicate have no value or that have no data related to value. Armstrong cautioned that "we don't want more regulation that would stifle innovation." There are many drugs available today without related biomarkers available, she said, and there is a need to "keep innovation and access to new technologies robust" in order to identify new diagnostics for these drugs.

The move toward accountable care organizations (ACOs) could advance the concept of value-based purchasing because those in the system would decide which test should be paid for, Armstrong said. In this system, the payment moves from the payer to the health care delivery system (perhaps an integrated one), and the decision can be made that sequencing a tumor has more value—both in terms of clinical outcomes and cost—than other options. However, Aetna has worked with ACOs, and none of them has yet incorporated genetics into its system because the ACOs are focused on public health priorities such as obesity and heart disease.

Decision-Support Tools

The value of decision-support tools in ACOs depends on the strength of the evidence, Armstrong said. "How strong does the evidence need to be that you have the confidence to recommend that this test be done or that you recommend a panel of multiple tests be done?" Payers are unlikely to recommend that multiple tests be done because of the potential for additional costs. Rather, decision making is likely to move, along with financial responsibility, to the managers of ACOs. The transition will not be uniform, she said. "There will be some groups that will be quicker, faster, smarter.

They will have a culture of genetics and oncology, and they will probably get to it first."

REIMBURSEMENT OF NEXT-GENERATION SEQUENCING

An NGS platform for whole genome or whole exome sequencing would provide more information than just a single companion diagnostic, which would present regulatory and reimbursement challenges, Terry said. Armstrong noted that when payers evaluate technologies, they do it individually. If a biomarker is safe, effective, and has clinical utility, it will be covered, she said. With a panel of tests that contains a biomarker of interest but other information as well, the additional information collected will not be covered unless it has been shown to be safe, effective, and useful, regardless of whether it was more cost-effective to order a whole panel versus a single test. "We have to start thinking differently about that, because genome sequencing is going to force us to do that," Armstrong said. "The question is, If cost is not a consideration, is there something inherently wrong with collecting information that you don't know what to do with?" In radiology, Armstrong said, students used to be taught not to look below the diaphragm on a chest X-ray because that was "fishing for trouble."

6

Concluding Observations

Important points were identified and potential solutions to the companion diagnostic and drug development pathway were offered by individual workshop participants and speakers throughout the day (see Box 6-1). These issues included the type of regulatory pathway that should be used for companion diagnostics, how clinical utility evidence could be generated, which payment models were likely to succeed, and how NGS could further transform thinking about companion diagnostics. The speakers identified several goals that, if met, could help facilitate the use of companion diagnostics in the future (see Box 6-2).

COORDINATING REGULATORY PATHWAYS

The discussion of IVDs and LDTs again raised the question of the economic incentive to develop companion diagnostics. As McCormack said, "The whole model will collapse unless the playing field is made level. Why would diagnostic companies want to invest years . . . and tens of millions of dollars to lose it shortly after you cross the finish line? It just doesn't make sense." Thompson agreed that this is an area for concern because in a system for generic diagnostics, FDA initially approves the companion diagnostic, and then a lab could decide to make a very similar test, validate it, and then sell it as a companion diagnostic for an associated drug. The pioneer of the test achieves FDA approval, but others can produce the same generic test that is subject to CLIA instead.

Several speakers reiterated the need to demonstrate the equivalence of IVDs and LDTs, in part through a follow-up of patients. CLIA is a law,

BOX 6-1
Possible Solutions for Co-Development Challenges Suggested by Individual Speakers

Workshop co-chair Debra Leonard highlighted suggested solutions and potential action items presented at the workshop by individual speakers.

- Regulatory oversight of LDTs is needed. This could be accomplished through a more robust CLIA accreditation process, a risk-based approach to regulation by FDA, or by choosing one path to assure the safety and effectiveness of all companion diagnostics, regardless of their source.
- Providing a mechanism to regulate follow-on tests may help provide more comparable economic incentives for IVD and LDT developers to produce diagnostics.
- In predicting drug response, rather than a particular test being specified, the companion diagnostic analyte and the performance characteristics of a test should be specified.
- The same molecular tests to diagnose and classify diseases could also be used for patient selection for drug clinical trials.
- Well-defined standards of evidence for the clinical utility of tests and the process for generating that evidence are needed for determining intended uses.
- It will be necessary either to demonstrate the equivalence of LDTs to FDA-approved companion diagnostics or else to rigorously monitor LDT performance, by making LDT performance data publicly available.

and thus LDTs are not going to go away or be subsumed under a single regulatory system without congressional legislation to do so, said Leonard. She recognized the need for greater regulatory oversight of LDTs, though she admitted that this would still not "level the playing field" between IVDs that go through the FDA approval process at significant expense and LDT developers. One possibility would be to formalize regulatory oversight of LDTs through a CLIA laboratory accreditation process, she said.

If a more robust CLIA is indeed a solution for regulating companion diagnostics, then part of that solution should be to eliminate FDA's role in regulating the tests because it would be duplicative, Thompson said. If an improved CLIA is "enough to assure safety and effectiveness of these tests, why wouldn't it be enough for all tests?"

One broadly discussed approach to demonstrating the equivalence of IVDs and LDTs, as well as to reducing variability in diagnostics, was the establishment of local or national testing and outcomes data repositories that would be used to gather and generate evidence to improve patient care. A workshop participant said that FDA has been discussing the possibility

BOX 6-2
Goals for Companion Diagnostics Identified by Individual Speakers

Workshop co-chair Debra Leonard summarized the goals for the future as presented by individual speakers during the workshop discussions. These goals were

- The development of a single test that could be used to simultaneously make a diagnosis, indicate treatment, and assess the adverse reaction risk for drugs upon clinical validation for each use.
- The creation of a global, value-based payment system for companion diagnostics (including next-generation-based testing) that would be based on evidence that considers overall patient care and achieving specific outcomes.
- A learning health care system, that, with research and payer support, uses clinical data to improve patient care moving forward.
- The establishment of a national testing and outcomes database to generate evidence for improving clinical care.
- The implementation of regulatory guidance for next-generation sequencing that would allow for the development of tests and would both direct patient care and be used for drug trials.
- The development of an FDA process to alter the drug label to account for cleared or approved new tests for existing or new drugs that would provide an alternative to requests that are now driven only by pharmaceutical companies.
- The institution of a new reimbursement method that would account for next-generation-based testing to provide more patient data at the same or at lower cost than multiple, individual diagnostic tests.

of such a database as a useful regulatory tool. Well-curated resources that contain genotype–phenotype information and other sorts of evidence would be extremely useful. It would also be practical, because similar resources are being developed for other purposes. A database could be used both for clinical interpretation of test results and for discovery, Leonard said. However, many laboratories may be reluctant to put the evidence that they generate into such a repository. Buller suggested starting small before deciding whether to increase the scale of the project and also creating incentives for laboratories to participate.

McCormack asked whether FDA should first triage all tests to determine which ones could be overseen by CLIA and which ones would need FDA approval. This approach would alleviate the burden of asking FDA to review the devices with less risk. A risk-based strategy would require

coordination between FDA and CLIA pathways to determine which tests go down which pathway, said Burke.

Gutman questioned whether FDA would be able to perform such a triage function, given its limited resources. In order to perform in such a way, FDA might need to use classification panels for assigning risks, and this process would likely need several years to be phased in, he estimated. A master file to record all tests could be established by an organization, with an independent body then suggesting which tests need the full approval process. However, no clear suggestion emerged of which organizations should be responsible for these roles—whether FDA, CLIA, or another body. Such lists are already maintained through CMS so that laboratories can be reimbursed for these tests, noted Victoria Pratt, chief director of molecular genetics at Quest Diagnostics at the time of the workshop, but the lists are not public.

Reducing Test Variability

Given how variable the results of tests can be, both tests performed in the same laboratory and tests done in different laboratories, the accuracy of all testing needs to be improved, said Buller. One possibility, he suggested, would be to create more centralized models for testing, perhaps involving consortia of hospitals. This might be especially useful in light of evidence suggesting that test accuracy improves with the number of tests a laboratory does. Another approach would be to define performance metrics for testing and then reward good performance and data transparency. Mansfield mentioned the possibility of establishing laboratories of excellence around the country where particular diagnostic tests would be sent. This would reduce variability because all laboratories would perform the same tests and could have the same performance levels.

GENERATING EVIDENCE FOR TEST VALUE

Leonard and Burke agreed that generating good evidence about how to get the right drug to the right patients at the right time remains a major issue and that randomized controlled trials will not be possible in all circumstances, which will require new study designs. Neither CLIA nor FDA formally assesses clinical utility, although payers are very interested in this issue, Leonard said. Payers try to make evidence-based decisions based on cost effectiveness and the quality of patient care and outcomes. However, payers generally do not have a coding system that allows them to distinguish between the use of a test in a setting where good evidence exists for the test's utility versus settings where such evidence does not exist. As a starting point, there is a way to generate robust evidence in the absence of a clinical trial by studying negative predictive markers to demonstrate negative clinical utility,

Robson said. The national testing database that was mentioned by Mansfield would also be a way to generate such evidence for determining test value.

Armstrong emphasized the need for high levels of evidence and standards surrounding tests, including LDTs, especially because even well-established tests can generate variable results. However, Mansfield raised the issue of follow-on tests where, because of a potential lack of clinical trial samples, it may be difficult to tell whether a test is better or worse than the original test. Buller agreed that retaining samples is usually unrealistic, but he also pointed out that discordant results are essentially doing the comparison. Is a false positive or false negative really false? Pfizer is making an effort to get clinical data whenever it supports a platform comparison in a particular country so that it can investigate these issues.

VALUE-BASED PRICING

Incentives are needed for the development and use of tests that improve patient outcomes and that move toward value-based payments, Burke said. Sharon Terry of the Genetic Alliance observed that value-based pricing for diagnostics is going to be an "extremely steep climb." Such pricing is unlikely to emerge from either the public or private sectors, she said; rather, it will emerge through business-to-business transactions among, for example, a diagnostic company, a pharmaceutical company, and an ACO. "Those are the only economic engines that are going to drive differential reimbursement," she said.

One of the barriers to value-based pricing is that the recipient of the value is not the person paying for the value, a workshop participant said. Given that situation, shifting health care costs toward individuals, as has been occurring in the recent past, could have its benefits. It could bring more rationality into the system if the recipients of health care have a louder voice in deciding what they are willing to cover out of their own pockets.

The development of national guidelines for clinical utility would be beneficial for the health care provider community in a value-based payment model, the workshop participant said. In a typical third-party-payer model, the payer makes the decision about reimbursement; however, in a bundled payment model, the payer and the provider have input on the decision making over reimbursement, another participant said. In the case with the bundled payment, if the payer does not have sufficient expertise in genetics, then the determination of value could rest on the provider. Armstrong said that an individual provider should not be relied on to take on all of the responsibility, but that it could be possible to make use of the collective expertise within the health care system for decision making about payments.

NEXT-GENERATION SEQUENCING

Next-generation sequencing will be a disruptive technology, and intended uses and proper interpretation will be critical, Gutman said. Armstrong suggested that next-generation sequencing will initially be used in clinical areas where it already makes sense, such as in the evaluation of infants in the newborn intensive care unit. She also pointed out that Aetna has a very small number of people who understand the detailed potential and problems of next-generation sequencing. "It would be good to get help," she said. "But we still have a fiduciary responsibility to administer a plan of benefits that a plan sponsor wants us to administer on their behalf. So we have to stick with technology assessments and evidence." Payers are not research organizations. They are claims payment organizations. They may study a few issues, but the full range of what needs to be evaluated is immense. "Health plans are not the solution to fill all these evidence gaps that exist," she said.

Finally, Swatkowski offered the perspective that companion diagnostics may be an interim step to understanding disease and mutations that are unique to particular patients. An all-encompassing diagnostic test would define "diagnosis, prognosis, and adverse reactions," and that is the NGS platform, she said.

Standards will be needed as next-generation sequencing gathers momentum, said Koch. Roche has begun doing next-generation sequencing, and it is finding a great deal of variation across platforms and analytical tools. "To ensure that we do the right things for patients and have accurate results, standards will be required, whether [tests] are LDTs or [FDA-approved] IVDs," Koch said, and he cautioned that next-generation sequencing is incredibly complex. "We have a challenge that is beyond technology here," he said. "It's really about how to understand the biology and appropriately translate it into something meaningful for patients."

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Appendix A

Workshop Agenda

Refining Processes for the Co-Development of Genome-Based Therapeutics and Companion Diagnostic Tests: A Workshop

February 27, 2013

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

Workshop Objective:

- To examine and discuss challenges and potential solutions for the co-development of targeted therapeutics and companion molecular tests for prediction of drug response.

8:30–8:35 A.M. **WELCOMING REMARKS**

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

Sharon F. Terry, Roundtable Co-Chair
President and Chief Executive Officer
Genetic Alliance

8:35–8:40 A.M. **Charge to Workshop Speakers and Participants**

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

8:40–10:05 A.M. **SESSION I: CO-DEVELOPMENT**

Moderator:

Victoria Pratt
Chief Director, Molecular Genetics
Quest Diagnostics Nichols Institute

8:40–9:00 A.M. **Effectiveness of Co-Development**

Felix Frueh
Entrepreneur-in-Residence
Third Rock Ventures

9:00–9:20 A.M. **FDA Review of Co-Development to Date**

Elizabeth Mansfield
Director, Personalized Medicine Staff
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health
U.S. Food and Drug Administration

9:20–10:05 A.M. **Discussion with Speakers and Attendees**

10:05–10:20 A.M. **BREAK**

10:20 A.M.–12:05 P.M. **SESSION II: CHALLENGES AND OPPORTUNITIES**

10:20–10:40 A.M. **Stakeholder Input on the Current Co-Development Paradigm**

Robert McCormack
Head, Technology Innovation and Strategy
Veridex LLC

10:40–11:20 A.M. **Stakeholder Presentations (10 minutes each)**

Discussion Moderator:

Geoffrey Ginsburg
Director, Center for Genomic Medicine
Institute for Genomic Sciences & Policy
Duke University

In Vitro Diagnostic Developers

Walter Koch
Vice President, Global Research
Roche Molecular Systems, Inc.

Pamela L. Swatkowski
Director, Regulatory Affairs
Abbott Molecular Inc.

Pharmaceuticals Developers

Scott Patterson
Executive Director, Medical Sciences
Amgen Inc.

Richard Buller
Vice President, Translational Oncology
Oncology Business Unit
Pfizer Inc.

11:20 A.M.–12:05 P.M. **Discussion with Speakers and Attendees**

12:05–12:55 P.M. **WORKING LUNCH**

12:55–1:45 P.M. **Stakeholder Presentations (10 minutes each)**

Discussion Moderator:

Patrick Terry
Founder
PXE International

Regulatory and Legal Oversight

Steven Gutman
Strategic Advisor
Myraqa, Inc.

Bradley Thompson
Member of the Firm
Epstein Becker & Green, P.C.

Payers

Bruce Quinn
Senior Health Policy Advisor
Foley Hoag, LLP

Joanne Armstrong
Senior Medical Director
Head, Women's Health
Aetna

1:45–2:40 P.M. **Discussion with Speakers and Attendees**

2:40–3:10 P.M. **Stakeholder Presentations (10 minutes each)**

Discussion Moderator:

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

Laboratory End Users

John Pfeifer
Vice Chair for Clinical Affairs, Pathology and Immunology
Professor, Pathology and Immunology
Professor, Obstetrics and Gynecology
Washington University School of Medicine

Clinical End Users

Sharon F. Terry
President and Chief Executive Officer
Genetic Alliance

Mark Robson
Clinic Director, Clinical Genetics Service
Department of Human Genetics
Memorial Sloan–Kettering Cancer Center

3:10–3:25 P.M. **BREAK**

3:25–4:10 P.M. **Discussion with Speakers and Attendees**

4:10–5:40 P.M. **SESSION III: POTENTIAL PATHS FORWARD**

4:10–4:25 P.M. **Pathways Toward Progress: Overview of Themes from the Day**

Debra Leonard, Workshop Co-Chair
Professor and Vice Chair for Laboratory Medicine
Director of the Clinical Laboratories
Weill Cornell Medical Center of Cornell University

4:25–5:40 P.M. **Advancing Co-Development**

Discussion Moderator:

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

Respondents

Pamela L. Swatkowski
Director, Regulatory Affairs
Abbott Molecular Inc.

Richard Buller
Vice President, Translational Oncology
Oncology Business Unit
Pfizer Inc.

Steven Gutman
Strategic Advisor
Myraqa, Inc.

Joanne Armstrong
Senior Medical Director
Head, Women's Health
Aetna

John Pfeifer
Vice Chair for Clinical Affairs, Pathology and Immunology
Professor, Pathology and Immunology
Professor, Obstetrics and Gynecology
Washington University School of Medicine

Mark Robson
Clinic Director, Clinical Genetics Service
Department of Human Genetics
Memorial Sloan–Kettering Cancer Center

5:40–5:50 P.M. **SESSION IV: CONCLUSION**

5:40–5:50 P.M. **Concluding Remarks**

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

Debra Leonard, Workshop Co-Chair
Professor and Vice Chair for Laboratory Medicine
Director of the Clinical Laboratories
Weill Cornell Medical Center of Cornell University

5:50 P.M. **ADJOURN**

Appendix B

Speaker Biographical Sketches

Joanne Armstrong, M.D., M.P.H., is a senior medical director for Aetna. Aetna is the nation's third largest health benefits company, serving over 16 million members. At Aetna, Dr. Armstrong leads the areas of women's health and genetics. In this role she is responsible for program development and implementation, quality assurance, medical cost management, and other activities. She is a board member of the Personalized Medicine Coalition. Dr. Armstrong is board certified in obstetrics and gynecology and has additional training in epidemiology and public health.

Richard E. Buller, M.D., Ph.D., is the vice president of translational oncology in the Pfizer oncology business unit. His group is responsible for development of biomarker and companion diagnostic clinical strategies as well as for proof of mechanism and pharmacology for drug candidates. The group's recent success is reflected by the approval of critoztinib for the treatment of ALK-positive non-small-cell lung cancer. Prior to joining Pfizer, Dr. Buller was vice president of translational medicine at Exelixis, Inc., a development-stage biotechnology company dedicated to the discovery and development of novel small-molecule therapeutics for the treatment of cancer and other serious diseases. At Exelixis his group played a central role in relating cancer drug effects in patients to drug targets and host genetics. Prior to the Exelixis position, Dr. Buller was a director in the Oncology Medicine Development Centre at GlaxoSmithKline (GSK), focusing on development and implementation of clinical strategies around the company's portfolio of oncology drug candidates. At GSK he co-led the successful supplemental new drug application for topotecan for the treatment of cervical cancer. Previously Dr.

Buller was a professor in the departments of obstetrics and gynecology and of pharmacology at the University of Iowa College of Medicine. He received a B.S. in chemistry from the University of California, Los Angeles, and was awarded both the doctor of medicine and doctor of philosophy (Bert O'Malley Lab) degrees from Baylor College of Medicine before completing an OB/GYN residency at the University of California, San Francisco, and a fellowship with Philip DiSaia at the University of California, Irvine. Dr. Buller is a board-certified gynecologic oncologist with extensive clinical trials experience in all phases of drug development, both as an academic and in industry. He is the author of more than 140 publications and has received numerous awards and honors, including multiple year listings in the Guide to America's Top Physicians prepared by the Consumer Research Council of America. His major laboratory research interest over the years has been the molecular genetics of ovarian cancer.

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 and Ethics (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 IOM 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 the 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 she is co-director of the Northwest-Alaska Pharmacogenomic Research Network.

W. Gregory Feero, M.D., Ph.D., obtained his M.D./Ph.D. from the University of Pittsburgh School of Medicine's medical scientist training program, with his Ph.D. in human genetics. He then completed his residency in family medicine at the Maine–Dartmouth Family Medicine Residency Program in Augusta, Maine. After 5 years in practice in Maine, Dr. Feero accepted a

position at the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH) as senior advisor to the director for genomic medicine under Drs. Francis Collins and Alan Guttmacher. He played a key role in coordinating NHGRI's activities related to family health history and was the planning chair for the NIH Consensus Development Program's 2009 State of the Science Conference "Family History and Improving Health." He also participated in efforts to help insure the appropriate representation of family health history and genomic data in electronic health records. Additionally, as chief of the Genomic Healthcare Branch in the Office of the Director, he oversaw efforts to advance genomics education for health professional disciplines including nurses, physician assistants, physicians, and pharmacists. In 2012 Dr. Feero stepped down from his position at NHGRI and continued on his role as research director and member of the faculty at the Maine–Dartmouth family medicine residency program. Currently he serves on the IOM Roundtable on Translating Genomic-Based Research for Health and as a contributing editor for the *Journal of the American Medical Association*. Dr. Feero sees patients four days a week in Fairfield, Maine, is board certified in family medicine, and holds professional licenses in Maine and West Virginia. He has authored numerous peer-reviewed and invited publications.

Felix W. Frueh, Ph.D., is president of the Medco Research Institute, leading Medco's real-world, outcomes-based research in personalized medicine. Dr. Frueh was associate director for genomics at FDA, managing partner at Stepoutside Consulting, and held senior positions at Transgenomic and Protogene Laboratories. He is a member of the board of the Personalized Medicine Coalition and TcLand Expression, Inc., and is an adjunct faculty member at the Institute for Pharmacogenomics and Individualized Therapy at the University of North Carolina. Dr. Frueh held faculty appointments in the departments of pharmacology and medicine at Georgetown University in Washington, DC, and was a fellow at Stanford University and the University of Basel, Switzerland, where he received his Ph.D. in biochemistry.

Geoffrey Ginsburg, M.D., Ph.D., is the founding director for genomic medicine at Duke University and assumed his current position in the Duke Institute for Genome Sciences and Policy in 2004. He is also the founding executive director of the Center for Personalized Medicine established in the Duke University Health System in 2010. He is currently professor of medicine and pathology at Duke University Medical Center. While at Duke, Dr. Ginsburg has pioneered translational genomics, initiating programs in genome-enabled biomarker discovery, longitudinal registries with linked molecular and clinical data, biomarker-informed clinical trials, and the development of novel practice models and implementation research for the

integration of genomic tools in heath care systems. With a strong commitment to interdisciplinary science he has led projects to develop predictive models for common complex diseases using high-dimensional genomic data as well as collaborations with engineering groups to develop novel point of care sensors. His work spans oncology, infectious diseases, cardiovascular disease, and metabolic disorders, and his research is addressing the challenges for translating genomic information into medical practice using new and innovative paradigms and the integration of personalized medicine into health care. He is an internationally recognized expert in genomics and personalized medicine with more than 200 published papers, and funding from NIH, the Department of Defense, the Defense Advanced Research Projects Agency, the Bill & Melinda Gates Foundation, and industry. In 1990 he joined the faculty of Harvard Medical School, where he was director of preventive cardiology at Beth Israel Hospital and led a laboratory in applied genetics of cardiovascular disease at Children's Hospital. In 1997 he joined Millennium Pharmaceuticals, Inc., as senior program director for cardiovascular diseases and was eventually appointed vice president of molecular and personalized medicine, where he was responsible for developing pharmacogenomic strategies for therapeutics as well as biomarkers for disease and their implementation in the drug development process. He has received a number of awards for his research accomplishments, including the Innovator in Medicine Award from Millennium in 2004 and the Basic Research Achievement Award in Cardiovascular Medicine from Duke in 2005. He is a founding member and former board member of the Personalized Medicine Coalition, a senior consulting editor for the *Journal of the American College of Cardiology*, an editor for *The HUGO Journal*, and an editorial advisor for *Science Translational Medicine*. In addition he is the editor of *Genomic and Personalized Medicine* (Elsevier), whose first edition was published in 2009. He has been a member of the Secretary of Veterans Affairs Advisory Council on Genomic Medicine and the National Advisory Council for Human Genome Research at NIH. He is currently an international expert panel member for Genome Canada; a member of the board of external experts for the National Heart, Lung and Blood Institute; a member of the IOM Roundtable on Translating Genomic-Based Research for Health; and a member of the external scientific panel for the Pharmacogenomics Research Network. He has recently been appointed to the advisory council for the newly established National Center for Advancing Translational Sciences at NIH. He has recently been nominated to serve on the World Economics Forum's Global Agenda Council on Personalized and Precision Medicine. Dr. Ginsburg received his M.D. and Ph.D. in biophysics from Boston University and completed an internal medicine residency at Beth Israel Hospital in Boston, Massachusetts. Subsequently, he pursued postdoctoral training in clinical cardiovascular medicine at Beth

Israel Hospital and in molecular biology at Children's Hospital as a Bugher Foundation Fellow of the American Heart Association.

Steven Gutman, M.D., M.B.A., is strategic advisor for Myraqa. He has more than 30 years of medical industry experience with more than 15 years at FDA, where he founded and directed the Office of In Vitro Diagnostics. Dr. Gutman holds a deep understanding of in vitro diagnostics history and regulation from developing policy and representing the agency for many years. Dr. Gutman came to Myraqa from the Blue Cross Blue Shield Association, where he extended his scope of work as an associate director, where he formed scientific valuations and policies. Dr. Gutman earned his M.D. at Cornell University Medical College, an M.B.A. with distinction from the State University of New York at Buffalo, and his B.S. from The Ohio State University.

Walter H. Koch, Ph.D., has been in his current role of vice president and head of global research for Roche Molecular Systems, Inc. (RMS) since 2005. As a member of the executive leadership team, he sits on the life cycle and business development committees and chairs the research portfolio committee. Dr. Koch is responsible for all Roche Molecular Diagnostics research and early development activities, including research efforts associated with biomarker discovery and validation, the development of new diagnostic platform technologies such as next-generation sequencing, and continuing improvements in the performance of existing real time polymerase chain reaction (PCR) products and technologies. He joined RMS in 1998 as a research leader to evaluate the feasibility of developing microarray-based pharmacogenetic assays for clinical diagnostic use, resulting in the launch of the AmpliChip® CYP450 assay. From 2001 to 2004 he served as the senior director of the pharmacogenetics department, leading six scientific teams and a bioinformatics group in the research and development of new genetics and genomics tests. In this role he was responsible for the development of genetic and pharmacogenomic assays using Affymetrix oligonucleotide microarray, linear array, and real-time kinetic PCR technologies and platforms. Prior to joining Roche he held several positions within FDA, including acting lab chief of immunochemistry and research biologist in the Center for Biologics Evaluation and Research Division of Transfusion Transmitted Disease as well as research biologist positions in the Division of Molecular Biological Research and Evaluation and the Division of Toxicology within the Center for Food Safety and Applied Nutrition. He received a B.S. in chemistry from Memphis State University and a Ph.D. in toxicology from the University of Tennessee, and he was a postdoctoral fellow within the Johns Hopkins University 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, which 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.

Elizabeth Mansfield, Ph.D., is the director of the personalized medicine staff in the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) in the Center for Devices and Radiological Health of FDA, where she is developing a program to address companion and novel diagnostic devices. She was previously a senior policy analyst in OIVD, managing policy and scientific issues. Dr. Mansfield formerly served as the director of regulatory affairs at Affymetrix, Inc., from 2004 to 2006. She previously served in other positions at FDA, including scientific reviewer and genetics expert. Dr. Mansfield received her Ph.D. from Johns Hopkins University and completed postdoctoral training at the National Cancer Institute and the National Institute for Arthritis, Musculoskeletal, and Skin Diseases.

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 start-up 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 its 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 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.

Scott D. Patterson, Ph.D., is an executive director in the medical sciences function at Amgen leading the In Vitro Diagnostic (IVD) Group, which is responsible for the identification, implementation, and management of diagnostic partnering strategies for all Amgen therapeutics (e.g., the development of KRAS as a predictive biomarker and companion diagnostic for Vectibix® therapy). The IVD Group builds upon Amgen's successful biomarker program, which Dr. Patterson led as head of molecular sciences for its first 8 years. He has published extensively in the field of proteomics and biomarkers, holds editorial board positions, and is a frequent guest lecturer. He was previously vice president of proteomics at the Celera Genomics Group and the chief scientific officer of Farmal Biomedicines, LLC. While at Celera, he established the company's initial foray into identification of cell surface targets for oncology, a number of which have been licensed. Dr. Patterson was at Amgen from 1993 to 2000, ultimately leading the Department of Biochemistry and Genetics. His academic career, which encompassed work on analytical protein chemistry applications and apoptosis, began at the University of Queensland, where he received his Ph.D. and B.Sc. while holding research positions of increasing responsibility over a period of 11 years, culminating in the position of senior research officer. In 1991 he joined the faculty of Cold Spring Harbor Laboratory, New York.

John Pfeifer, M.D., Ph.D., is the vice chairman for clinical affairs and a professor in the Department of Pathology and Immunology at the Washington University School of Medicine in St. Louis. He is board certified in anatomic pathology and subspecialty board certified in molecular genetic pathology, and he has been a practicing surgical pathologist for more than 20 years. His academic interests are primarily focused on investigating the role of molecular genetic testing in the analysis of tissue specimens, specifically on the methods and clinical settings in which molecular testing provides inde-

pendent information that increases diagnostic accuracy or provides more accurate prognostic estimates or can be used to guide therapy.

Victoria M. Pratt, Ph.D., is a medical and clinical molecular geneticist board certified by the American College of Medical Genetics. She is currently chief director, molecular genetics, for Quest Diagnostics. In addition to her work for Quest Diagnostics, Dr. Pratt served on the U.S. Secretary of Health and Human Services Advisory Committee on Genetics, Health, and Society for the Oversight of Genetic Testing. She also participated in the preparation of the *Morbidity and Mortality Weekly Report* publication on best practices in molecular genetic testing for the Centers for Disease Control and Prevention (CDC). Dr. Pratt continues to serve on the CDC's GeT-RM program for reference materials for molecular genetics. She is currently serving on the U.S. Secretary of Health and Human Services Advisory Committee on Hereditary Disorders in Newborns and Children. Dr. Pratt is past chair of the clinical practice committee and is currently a member of the professional relations committee for the Association for Molecular Pathology and is an advisory member of EurogenTest for genetic test validation. She also is a member of the Quest Diagnostics best practice team for quality control. Dr. Pratt has authored more than 40 peer-reviewed manuscripts and book chapters. She continues to be involved in genetics training and holds a faculty appointment at NIH. Dr. Pratt is the associate editor for the *Journal of Molecular Pathology*. Dr. Pratt graduated with a Ph.D. in medical and molecular genetics from Indiana University School of Medicine in Indianapolis in 1994. Her fellowship training was in medical and clinical molecular genetics at Henry Ford Hospital in Detroit, Michigan.

Bruce Quinn, M.D., Ph.D., is the senior health policy advisor with Foley Hoag LLP. Dr. Quinn 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. He has written a series of authoritative white papers on evolving Medicare policy for genomic tests in 2012–2013, and he authored the reimbursement chapter in the authoritative handbook *Genomic and Personalized Medicine* (Academic Press, 2012). 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 and life sciences division of Accenture, working with the pharmaceutical, biotechnology, and genomics industries. Dr. Quinn is a board-certified pathologist who held physician-scientist faculty positions at New York University and Northwestern University. The author or co-author of more than 30 scientific publications, he also holds an M.B.A. from the Kellogg School of Northwestern University.

Mark Robson, M.D., is an associate attending physician of the Clinical Genetics and Breast Cancer Medicine Services in the Department of Medicine at Memorial Sloan–Kettering Cancer Center. He received his B.Sc. from Washington and Lee University and his M.D. from the University of Virginia. He performed residency and fellowship training at Walter Reed Army Medical Center before coming to Memorial Sloan–Kettering in 1996. He is currently the clinic director of the Clinical Genetics Service and the immediate past chair of the Cancer Genetics Subcommittee of the Cancer Prevention Committee of ASCO. Dr. Robson's research is primarily directed toward the improving the integration of genetic information into the clinical management of women with breast cancer. He and his colleagues have conducted a number of studies examining outcomes in women with hereditary breast cancer to better define the risks and benefits of treatments such as breast-conserving therapy and adjuvant chemotherapy in this group. He and his coworkers have also conducted a number of studies examining the effectiveness of screening interventions such as breast magnetic resonance imaging or ovarian cancer screening in women at hereditary risk. He is currently conducting studies to evaluate the impact of intensive screening or surgical prevention upon women's quality of life, and to develop new screening tools, such as serum peptide profiling. He is also investigating the optimal integration of new genetic technologies, such as genomic profiling, into the care of women at risk for breast cancer.

Pamela L. Swatkowski, B.S., is director of regulatory affairs at Abbott Molecular, where she is responsible for strategic regulatory programs including companion diagnostics regulatory and business development support, product lifecycle management, and global product registration filings for the molecular diagnostics product line. She has more than 25 years of experience in regulatory affairs, Ms. Swatkowski received a bachelor of science degree in biology in 1983 from Loyola University of Chicago. Ms. Swatkowski began her career at Abbott in the diagnostics division in research and development in 1983 and rejoined the company in 2004 with Abbott Molecular. In addition, she has worked at Nalge Nunc International, a ThermoFisher company in several regulatory and quality leader-

ship roles. Ms. Swatkowski has a passion for personalized health care and works toward communication and conveying the importance of companion diagnostics products that are beneficial to the patient.

Sharon Terry, M.A., is president and chief executive officer of the Genetic Alliance, a network of more than 10,000 organizations, 1,200 of which are disease advocacy organizations. Genetic Alliance improves health through the authentic engagement of communities and individuals. It develops innovative solutions through novel partnerships, connecting consumers to smart services. Ms. Terry is the founding chief executive officer of PXE International, a research advocacy organization for the genetic condition pseudoxanthoma elasticum (PXE). As co-discoverer of the gene associated with PXE, she holds the patent for ABCC6 and has assigned her rights to the foundation. She developed a diagnostic test and is conducting clinical trials. Ms. Terry is also a co-founder of the Genetic Alliance Registry and Biobank. She is the author of more than 90 peer-reviewed articles. In her focus at the forefront of consumer participation in genetics research, services, and policy, she serves in a leadership role on many of the major international and national organizations, including the IOM Health Sciences Policy Board, the National Coalition for Health Professional Education in Genetics board, and the International Rare Disease Research Consortium Interim Executive Committee, and she is a member of the IOM Roundtable on Translating Genomic-Based Research for Health. She is on the editorial boards of several journals. She was instrumental in the passage of the Genetic Information Nondiscrimination Act. She received an honorary doctorate from Iona College in 2005 for her work in community engagement, the first Patient Service Award from the University of North Carolina Institute for Pharmacogenomics and Individualized Therapy in 2007, the Research!America Distinguished Organization Advocacy Award in 2009, and the Clinical Research Forum and Foundation's Annual Award for Leadership in Public Advocacy in 2011. She is an Ashoka Fellow.

Bradley M. Thompson, J.D., is a shareholder in the law firm of Epstein Becker & Green, P.C. There he counsels medical device, drug, combination product, and biotechnology companies on a wide range of FDA regulatory, reimbursement, and clinical trial issues. At the firm Mr. Thompson leads the medical device regulatory practice, the clinical trials practice, and the connected health practice, and he serves on the firm's health and life sciences steering committee. For trade associations Mr. Thompson has served as counsel to AdvaMed and the Continua Health Alliance; as general counsel to the Combination Products Coalition, mHealth Regulatory Coalition, and the Clinical Decision Support Coalition; and as general counsel and secretary for the Indiana Medical Device Manufacturers Council. Mr. Thompson

has taught food and drug law at Indiana University School of Law–Indianapolis and at Columbia Law School. He also serves on the editorial boards for *Medical Device & Diagnostic Industry* (since 1993), *Food & Drug Law Journal* (since 2007), and BNA's *Medical Device Law & Industry Report* (since 2007). Mr. Thompson also serves as co-chair of the food and drug law committee in the American Bar Association and of the medical device committee of the Food and Drug Law Institute (FDLI). Mr. Thompson has written extensively on the topics of medical device regulation, including a book titled *FDA's Regulation of Medical Devices* (Interpharm Press, 1995), and has co-authored chapters in *Off-Label Communications: A Guide to Sales and Marketing Compliance* published by FDLI (2008–2009) and in a book titled *Guide to Medicare Coverage Decision-making and Appeals* published by the American Bar Association (2002). Mr. Thompson was included in 100 Notable People in the Medical Device Industry (*Medical Device & Diagnostics Industry*, June 2004), has earned an AV rating in Martindale-Hubbell (its highest rating), has been named a "SuperLawyer" in Indiana, has been elected as a fellow in the American Bar Foundation, and is listed in *A Guide to America's Leading Business Lawyers* from Chambers USA. Mr. Thompson received his B.A. cum laude and an M.B.A. from the University of Illinois and his J.D. cum laude from the University of Michigan Law School.

Appendix C

Statement of Task

An ad hoc planning committee will plan and conduct a public workshop to examine and discuss challenges and potential solutions for the co-development of targeted therapeutics and companion molecular tests for prediction of drug response. The goal of the workshop will be to feature presentations and advance discussions among a broad array of stakeholders which may include in vitro diagnostic test companies, pharmaceutical companies, regulators, pathologists, providers, patients, and public and private payers. 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

Brian Abbott
AstraZeneca

Hesham Abdullah
MedImmune

Deborah Applebaum-Bowden
National Heart, Lung, and Blood Institute

Joanne Armstrong
Aetna

Euan Ashley
Stanford University

Eric Assaraf
WRG

Stephanie Beasley
FDA Week

Judith Benkendorf
American College of Medical Genetics and Genomics

Paul Billings
Life Technologies

Giselle Bleecker
Medical Market Strategists, Inc.

Bruce Blumberg
Kaiser Permanente

Jeffrey Bojar
Biodesix

Denise Bonds
National Heart, Lung, and Blood Institute

Mary Bordoni
Personalized Medicine Coalition

Khaled Bouri
U.S. Food and Drug Administration

Christopher Bradburne
Johns Hopkins University, Applied Physics Laboratory

Pamela Bradley
U.S. Food and Drug Administration

Joel Brill
Predictive Health, LLC

Apryl Brown
Wayne County Community College District

Heather Brown
Blue Cross Blue Shield Association

Richard Buller
Pfizer Inc.

Wylie Burke
University of Washington

Khatereh Calleja
AdvaMed

Joseph Campbell
National Institute of Allergy and Infectious Diseases

Carolyn Carroll
STAT TECH Inc.

Cathy Craft
Myraqa, Inc.

Sean David
Stanford University

Ulyana Desiderio
American Society of Hematology

Patricia Deverka
Center for Medical Technology Policy

Michael Dougherty
American Society of Human Genetics

Victor Dzau
Duke University Health System

Raith Erickson
Complete Genomics

Raith Ewing
Johns Hopkins University

Ross Filice
U.S. Food and Drug Administration

Felix Freuh
Third Rock Ventures

Edna Garcia
American Society for Clinical Pathology

John Gardenier
Independent

Turkan Gardenier
Pragmatica Corp

Geoffrey Ginsburg
Duke University

Monica Gonzalez
The George Washington University

Federico Goodsaid
Vertex Pharmaceuticals

Klaus Gottlieb
U.S. Food and Drug Administration

Steven Gutman
Myraqa, Inc.

Natalie Hamm
American Cancer Society Cancer Action Network

Kim Harp
Mary Breckinridge School of Nursing

Gerald Higgins
AssureRX Health, Inc.

Richard Hodes
National Institutes of Health

Laurie Huard
Precision Therapeutics, Inc.

Dora Hughes
Sidley Austin, LLP

Sam Johnson
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Rasika Kalamegham
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