Systems for Research and Evaluation for Translating Genome-Based Discoveries for Health: Workshop Summary

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SYSTEMS FOR RESEARCH AND EVALUATION FOR TRANSLATING **GENOME-BASED DISCOVERIES** FOR HEALTH

W O R K S H O P S U M M A R Y

Theresa Wizemann, *Rapporteur*

Roundtable on Translating Genomic-Based Research for Health

Board on Health Sciences Policy

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

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

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Dennis W. Choi, Comprehensive Neuroscience Initiative, Emory University, Atlanta, GA. Appointed by the Institute of Medicine, he was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the author and the institution.

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The Roundtable wishes to express its gratitude to the expert speakers whose presentations examined existing systems that create the kinds of resources and structure that facilitate evaluation of genome-based health care. These speakers are Alfred O. Berg, Ralph G. Brindis, Wylie Burke, Robert L. Davis, Geoffrey Ginsburg, Sharon Kardia, Sumitra Muralidhar, James M. Perrin, Kathryn A. Phillips, Bruce Quinn, Sharon Terry, Steven Teutsch, and Marc S. Williams.

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Introduction

> The sequencing of the human genome has generated excitement about the potential of genomic innovations to improve medical care, preventive and community health services, and public health. (IOM, 2008)

How variations in genes contribute to variations in disease risk has been a subject of study for more than 100 years (IOM, 2006). Until fairly recently research focused on single genes that give rise to rare genetic diseases such as cystic fibrosis or Huntington's disease. With the advent of genome-wide association (GWA) studies, however, numerous associations between specific gene loci and complex diseases have been identified, for example for breast cancer, type II diabetes, coronary artery disease, asthma, and bipolar disorder (Goldstein, 2009; Hardy and Singleton, 2009; Smith and Lusis, 2009).

This rapidly advancing field of genomics has stirred great interest in "personalized" health care from both the public and private sectors. The hope is that using genomic information in clinical care will lead to reduced health care costs and improved health outcomes as therapies are tailored to the genetic susceptibilities of patients. A variety of genetically based health care innovations have already reached the marketplace, but information about the clinical use of these treatments and diagnostics is limited. While GWA studies provide information about an association between a gene and a trait or disease, these data do not provide information about how a genomic test or other innovation impacts clinical care and patient health outcomes—other approaches are needed to garner such information.

The Institute of Medicine's Roundtable on Translating Genomic-Based

Research for Health identified a need for a workshop to examine existing systems that could be adapted to evaluate the clinical use and impact of genetically based innovations in patient care.[1] Established in 2007, the Roundtable seeks to foster dialogue and partnerships that will advance the field of genomics and improve the translation of basic genomic research to health care, education, and health policy. On February 12, 2009, the Roundtable convened a workshop designed to address four central questions related to the development of systems to evaluate clinical use of health care innovations that stem from genome-based research:

- What are the practical realities of creating such systems?
- What different models could be used?
- What are the strengths and weaknesses of each model?
- How effectively can such systems address questions about health outcomes?

The following chapters summarize the presentations by the expert panelists, and the open discussions moderated by Roundtable Chair Wylie Burke. Chapter 2 provides an overview describing how the evidence needed for decision making may vary according to the particular application of the genome-based intervention. Chapters 3 through 5 summarize the three panel sessions: creating evidence systems; current practices in moving from evidence to decision; and gaps in the system for evaluation of genome-based health care. Closing remarks are provided in Chapter 6, and the workshop agenda and biographical sketches of the panelists are available in the appendixes.

[1] The planning committee's role was limited to planning the workshop. This workshop summary has been prepared by a rapporteur as a factual summary of what occurred at the workshop. Statements and opinions are those of individual presenters and participants, and should not be construed as reflecting any group consensus.

2

Generating Evidence for Decision Making

DOES THE TYPE OF DECISION BEING MADE INFLUENCE THE EVIDENCE NEEDED?

Steven Teutsch, M.D., M.P.H.
County of Los Angeles Department of Public Health

Decisions affecting health care must be acceptable and legitimate to the people they will affect, Teutsch began. The legitimization of health policy decisions requires prospective agreement about the evidentiary standards that will be used. This is a deliberative and inclusive process to develop an understanding of the different types of decisions to be made, and the nature and importance of the evidence that is appropriate for each. There is no simple formula or prescription for decision making. Each decision is based not only on the evidence, but also the context in which each decision is being made. Transparency of the process is also important, so that it is clear what information was used in making the decision.

Evidentiary Threshold

The translational process can be viewed as moving from gene discovery to application in a health context, to health practice, and finally to understanding the health impact (Figure 2-1). The critical step in translation is the development of an evidence-based guideline that allows the technology to move from research into clinical or public health practice. A key question

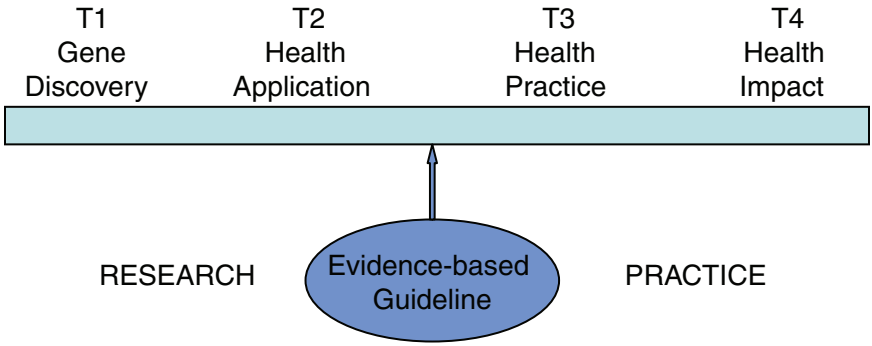

FIGURE 2-1 The translational process.
SOURCE: Teutsch, 2009.

in developing guidelines, Teutsch said, is how high the evidence bar should be. By employing a lower threshold, technologies can move more rapidly from research into practice. The consequences are that less information is available on the clinical validity of the technology, and almost no information is available about the clinical use. This lack of information can lead to negative insurance coverage decisions. There is the potential for increased harms because less is known about the technology, but also the potential for increased benefits by providing the technology sooner to those who may need it. Requiring a lower evidentiary bar means a greater dependence on models and expert opinion. Because technologies can enter practice more easily, a lower bar might stimulate innovation, thereby making more technologies available.

If the evidentiary bar is high, more will be known about the validity and utility of the technology, and payers can make better decisions about reimbursement. On the other hand, a higher threshold for evidence makes moving technologies into practice more difficult, which can potentially lower the incentive for innovation. More is known about the technology, resulting in a diminished potential for harms, but it will take a longer time to bring the product to those who can benefit from it.

When making an evidence-based decision, several questions must be answered:

- What decision must be made?
- How does the nature of that decision affect the evidentiary standards that should be applied?
- What are the relevant contextual issues?

- How will information (both scientific and contextual) be integrated and applied?
- What processes are needed to legitimize the decision process?

There is a dynamic relationship between evidence-based decision making and evidence review and synthesis (Figure 2-2). Decisions may pertain to regulation, coverage, guidelines, quality improvement metrics (e.g., pay-for-performance), or individual care decisions made by a clinician and/or patient. The decision maker should first frame the key questions to be answered and determine the level of rigor required. Then evidence reviewers should synthesize data from studies as well as desired economic information. With quantitative scientific evidence in hand, the decision makers should also consider budget constraints, values and preferences, equity issues, acceptability, and other contextual issues before making a decision.

Quantitative Information for Decision Making

Quantitative information needed for decision making includes data on effectiveness, such as the level of certainty there will be an impact, and the magnitude of the effect, or net benefit. Cost and cost-effectiveness data are

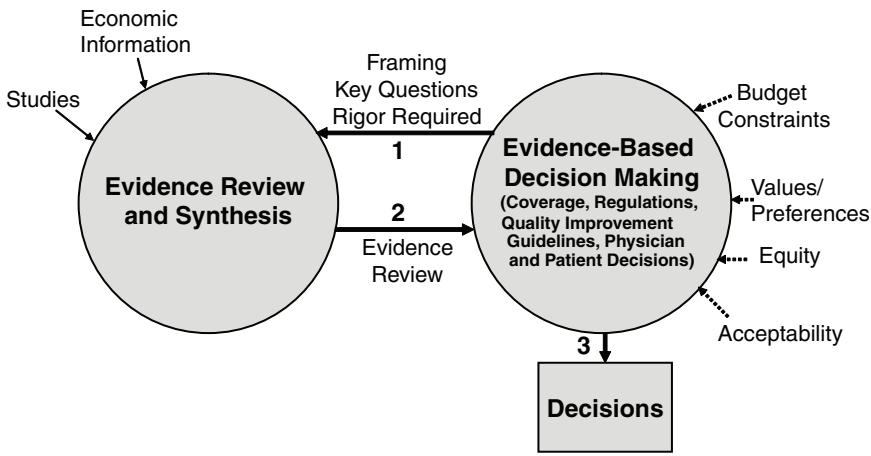

FIGURE 2-2 Dynamic relationship between evidence review and synthesis and evidence-based decision making.
SOURCE: Teutsch and Berger, 2005.

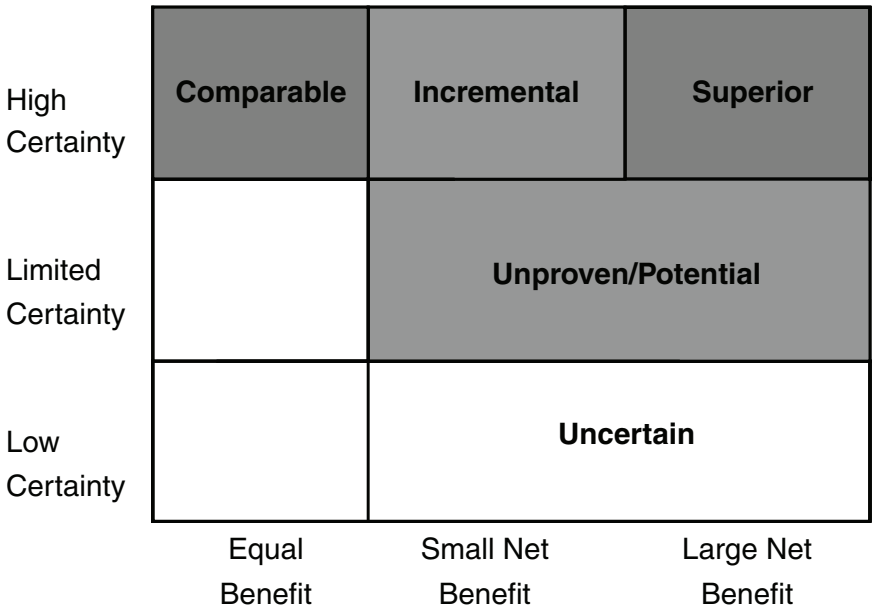

FIGURE 2-3 Comparative clinical effectiveness matrix.
SOURCE: Developed by the America's Health Insurance Plans (AHIP) Evidence Based Medicine Roadmap Group, Personal communication, S. Pearson, Institute for Clinical and Economic Review (ICER), July 9, 2009.

also important, as are any data regarding how the new technology compares to existing alternatives. Clinical effectiveness and cost effectiveness are usually assessed in relationship to therapeutic or diagnostic alternatives.

A matrix, such as the one under development by America's Health Insurance Plans, can be useful to help payers compare two technologies with regard to net benefit and certainty (Figure 2-3). Technologies that have large net benefit and high certainty would be good candidates for coverage. On the other hand, products with limited or low certainty and equal net benefit are not ready for broad use. Some will have incremental benefits, but high certainty, and others will have new technology that is unproven, but has potential. Different insurance groups are likely to make different coverage decisions. Payers should be able to articulate what their criteria are, or how high the evidentiary bar is going to be, so a technology developer can decide whether to invest in developing the technology.

The key effectiveness questions relate to the following:

- Efficacy: Can the technology work in controlled conditions?
- Harms: What are the possible harms?
- Effectiveness: Does it work in practice?
- Trade-offs: What is the balance of harms and benefits?
- Comparative effectiveness: Does it work better than alternatives currently in use?
- Subpopulations: Are there specific groups for whom it is likely to be a technology of choice?

As one example of a framework to determine how high the evidentiary bar should be for clinical management decisions, Teutsch cited the work of Djulbegovic and colleagues (2005) on cancer. The framework lays out proposed evidentiary standards for clinical applications as a function of treatment goals and acceptable regret. Considering the various goals of treatment—including cancer prevention in healthy individuals, palliative therapies, procedures that offer incremental improvement in terms of survival, or curative measures—how much certainty is needed before a technology should be used? How much regret will there be if the technology used is ineffective or even harmful?

In the prevention arena, Teutsch said, the evidentiary bar is very high because the interventions are being delivered to people who are otherwise healthy. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group, established by the Centers for Disease Control and Prevention, recently published its methods for evidence-based evaluation of genetic tests (Teutsch, 2009). Genome-based products first were categorized by application: diagnostic, screening, risk assessment and susceptibility, prognostic, or predicting therapeutic response. EGAPP then established the criteria that would be used when assessing clinical validity and utility issues (Table 2-1).

One approach to answering the quantitative questions is the ACCE model for evaluating data on emerging genetic tests. The model breaks down the information needed into four main areas (from which the name is derived): Analytic validity, Clinical validity, Clinical utility, and Ethical, legal, and social implications (Haddow and Palomaki, 2004). At the center of the circle in Figure 2-4 is the disorder to which the genetic test will be applied, and the setting in which the testing will be done. From there, an analytic framework is constructed by answering more than 40 targeted questions in each of the 4 areas.

EGAPP has been working within the ACCE framework to articulate the evidentiary standards that could or should be applied to evaluation of genetic tests. Table 2-2 presents a hierarchy of data sources and study designs for the analytic validity, clinical validity, and clinical utility compo-

TABLE 2-1 Categories of Genetic Test Applications and Some Characteristics of How Clinical Validity and Utility Are Assessed

Application	Clinical Validity	Clinical Utility
Diagnosis	Association with disorder	Improved clinical outcomes Usefulness for decision making End of diagnostic odyssey
Disease screening	Association with disorder	Improved health outcome Usefulness for decision making
Risk assessment/ susceptibility	Association with future disorder	Improved health outcomes
Prognosis of diagnosed disease	Association with natural history	Improved health outcomes, or outcomes of value to patients, based on changes in patient management
Predicting treatment response	Association with a state that relates to drug efficacy or Adverse Drug Experiences	Improved health outcomes or adherence based on drug selection or dosage

SOURCE: Adapted from Teutsch et al., 2009.

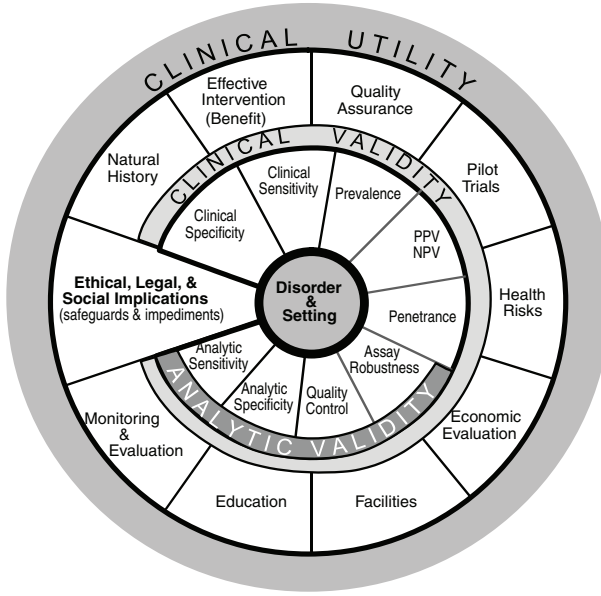

FIGURE 2-4 The ACCE method for multidisciplinary evaluation of genetic tests.
SOURCE: CDC, 2007.

TABLE 2-2 Hierarchies of Data Sources and Study Designs for the Components of Evaluation

Level	Analytic Validity	Clinical Validity	Clinical Utility
1	Collaborative study Summary data from well-designed external proficiency testing	Well-designed longitudinal cohort studies Validated clinical decision rule	Meta-analysis of RCTs
2	Other proficiency testing Well-designed peer-reviewed studies Expert panel reviewed FDA summaries	Well-designed case-control studies	A single RCT
3	Less well-designed peer-reviewed studies	Lower quality case-control and cross-sectional studies Unvalidated clinical decision rule	Controlled trial without randomization Cohort or case-control study
4	Other research, clinical laboratory or manufacturer data Studies on performance of the same basic methodology	Case series Other research, clinical laboratory or manufacturer data Consensus guidelines Expert opinion	Case series Other studies, clinical laboratory or manufacturer data Consensus guidelines Expert opinion

SOURCE: Teutsch, 2009.

nents of evaluation. Looking at clinical utility, for example, meta-analysis of randomized controlled trials (RCTs) would be the strongest form of evidence. A good single RCT may be adequate, but less strong. The list then covers other study designs that are progressively less desirable, such as controlled trials that are not randomized, or cohort studies, with case series or expert opinion being the least desirable form of evidence.

Contextual Information for Decision Making

Numerous contextual issues can inform the decision to introduce a test into practice. Clinical applications differ widely, and it is important to consider the severity of the condition, subgroup differences, the availability of alternatives, the severity and frequency of harms, and the risk of overuse or inappropriate use of the test. Economics is also considered from

a contextual perspective. Many decision makers are interested not only in cost-effectiveness, but also budget impact, budget constraints, and value. Legal and ethical considerations include federal and state regulatory constraints, as well as issues of precedent, and regret as a result of introducing or not introducing a test. Feasibility of the test in question refers to the current level of use, the infrastructure required to use the test properly, and the acceptability of the test to all partners and stakeholders, particularly patients. Decisions should be made in the context of the preferences and values of those who are going to be affected by the decision. Finally, there are administrative issues, such as options for targeting or limiting the use of the test to patients who would benefit most, and how to consider possible further evidence.

Decision-Factor Matrix

In the end, Teutsch said, a systematic process is needed to ensure fairness and reasonableness in decision making. This process includes: clear "rules of the road" for the technology developers, patient advocacy groups, and others; a deliberative process incorporating both quantitative and qualitative or contextual information; transparency; and an appeals processes so that when other issues arise, they can be addressed, and the decision changed where appropriate.

Teutsch presented a draft of a decision matrix, plotting different decisions that are likely to be made for any test or technology against a set of quantitative and qualitative information that might need to be generated. His example (Figure 2-5) suggests that a regulator may be primarily interested in efficacy, safety, and the legal and ethical constraints. These aspects, however, would be less likely to impact individual decisions. Rather, effectiveness, as well as cost, may be of great interest in practice. Each type of user will have important criteria, some secondary considerations, and other information that may not be directly relevant. The important point, Teutsch said, is that different decision makers require different kinds of information, and it is important to be able to generate that information for them.

In refining the approach to standards of evidence, Teutsch said in conclusion, it will be important to rethink the hierarchy of evidence in terms of the many different applications and new types of evidence. When is it appropriate to use predictive modeling, for example? Another critical issue is how research efforts are aligned with application needs. The evolving role of observational data must be accommodated, and appropriate methods must be used to make better decisions when the evidence is insufficient.

	Regulation	Coverage	Guidelines	Quality Improvement	Individual Decisions
Efficacy					
Safety					
Effectiveness					
Comparative Effectiveness					
Cost/ Cost Effectiveness					
Clinical Situation					
Legal/Ethical					
Values/Preferences					
Admin.*					
Feasibility					
Stakeholders					

FIGURE 2-5 Example of a hypothetical decision-factor matrix.
* Administrative feasibility of management, e.g., limiting coverage to people who meet specific criteria.
Legend:
White: primary consideration.
Light grey: secondary consideration.
Dark grey: minor or no consideration.
SOURCE: Teutsch, 2009.

DISCUSSION

Wylie Burke, M.D., Ph.D.
Moderator

A question was asked as to whether the appeals process mentioned by Teutsch would address passive challenges, such as a need for change identified as a result of horizon scanning, as well as active challenges. Teutsch responded that there may be information that was not taken into consideration in the original decision, and the appeals processes can help address that issue. But in general, one should be proactive about the information generation process. In trial design, for example, it is important to ensure representation from the appropriate groups, and that may require participation of the affected groups in the development of the study.

A participant noted that the methodology outlined focuses on the test or the technology itself, and asked if the questions would change when the

focus was on whether or not to screen for a condition. Teutsch responded that one needs to have a specific clinical scenario in mind, and that assessments should not be done in the abstract.

Another participant expressed concern about the decision matrixes considering low efficacy and harm as if they were similar in impact, and suggested that a distinction be made. Teutsch said the vocabulary varies, but in his perspective, efficacy refers to benefits, and effectiveness refers to the balance of the benefits and potential harms. On some occasions, risk of substantial harm may be acceptable because of the potential for substantial benefits, while at other times the equation will be different. He agreed there is a need to be clear about whether one is talking about benefits or harms, and to whom they accrue.

3

Creating Evidence Systems

For the first panel session, speakers were asked to address four questions: (1) What are your goals for genetic research? (2) How do you decide what studies to pursue? (3) What barriers did you overcome, or do you still face, in your research? (4) What are the greatest challenges for translation of genomics research going forward?

HMO RESEARCH NETWORK

Robert Davis, M.D., M.P.H.
Center for Health Research Southeast, Kaiser Permanente Georgia

The HMO Research Network (HMORN) is a consortium of 15 health maintenance organizations (HMOs) that collectively cover about 11 to 15 million health plan members. The goal of the network is to facilitate collaborative research aimed at improving health and health care. To that end, the Network recently formed a Pharmacogenomics Special Interest Group. Davis noted that over the past 10 years, there has been an emerging consensus on what the important issues are related to genetic testing and pharmacogenomics. One key issue is the concept of clinical utility. By the time a gene-based test is evaluated, the issues of clinical validity have generally been addressed, but not necessarily clinical utility. Clinical utility, Davis said, really means clinical outcomes. Davis cited several publications

that discuss how to assess the impact of pharmacogenomics and evaluate the benefit and risk of new genome-based technology (Burke and Zimmern, 2004; Califf, 2004; Davis and Khoury, 2006; Grosse and Khoury, 2006; Khoury et al., 2008; Phillips, 2006).

An evidence-based framework to evaluate the clinical utility of new genetic tests and treatments is lacking in the current health care infrastructure. The goal of genome-based research is personalized delivery of therapeutics that account for the genetic variation of the patient. This is a long-term new direction in medicine that, Davis said, will play out over many years. Researchers have just begun to see how complicated the genome is. There is much to be learned about the role of polymorphisms, age-dependent changes, methylation, *de novo* mutations, or gene copies, for example.

Gene-based diagnostic tests are very powerful. They have distinctive risk/benefit profiles, and may have significant unintended effects. Historically, however, genetic tests have been held to a less stringent regulatory standard than pharmacogenetic drugs, which require evidence of improved clinical outcomes to receive Food and Drug Administration approval. Davis stressed that the default for gathering evidence on gene-based diagnostic tests and therapeutics should be a randomized controlled trial (RCT). If an RCT is not feasible, and many times it will not be due to lack of financial and human resources, then population-based observational studies should be conducted.

HMOs, such as Kaiser, evaluate new genetic technologies in similar fashion to what has been done previously for other types of technologies. The first step is to determine if there is good evidence, either from RCTs or observational data, that the technology improves outcomes. Based on a review of the evidence, for example, HMOs are now conducting gene testing for HER-2/neu status of breast cancer tumors. However, a decision about whether to conduct gene testing for polymorphisms involved in the metabolism of the anticoagulant warfarin is still under consideration, pending the results of an ongoing RCT. The second step is to determine whether the new technology improves outcomes in a cost-effective manner. There are no set criteria for what reasonable cost is, and cost is considered relative not only to money, but also to resources and time. An example of a new test that has been determined to be cost effective is the screening test for the presence of the HLA-B*5701 allele that has been shown to be associated with hypersensitivity to the antiretroviral drug abacavir. The results of an RCT (Mallal et al., 2008) showed that HLA-B*5701 screening had a negative predictive value of 100 percent, and a positive predictive value of 47.9 percent, and estimated that 1 out of every 25 to 30 Caucasians will be hypersensitive to abacavir, leading Kaiser to conclude that this test would be cost effective.

Collaborative Studies

The lack of data to support integrating new genetic tests and technologies into practice is a major challenge. In gathering this evidence, HMORN, like many research organizations, is primarily opportunistic. HMORN has formed joint informal collaborations with the Pharmacogenomic Research Network (PGRN), which is funded through the National Institute of General Medical Sciences, and with the Agency for Healthcare Research and Quality (AHRQ) Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) network. The goal of these collaborations is to bridge the divide between researchers and decision makers, and to collect the evidence needed to inform decisions on whether to adopt a gene-based test into practice. A number of studies are under way to examine genetic variation in response to metformin, statins, and asthma-related drugs (primarily beta agonists and steroids). An informal decision-making process is used to decide which drug classes to study. These drugs were selected for study because substantial morbidity and mortality are associated with diabetes, cardiovascular disease, and respiratory illness, especially in children, and treating these diseases is costly. The studies are feasible because there are a substantial number of exposed patients, and studies large enough to have statistical power can be conducted at a single site. Importantly, recent advances in science have made it possible to study the clinical impact of testing for these genetic polymorphisms in population-based settings.

For nearly 10 years, the PGRN has been focused on discovery of gene polymorphisms that influence the response to certain medications. HMORN is now conducting a case-control study to investigate the role of these gene polymorphisms in predicting response to drugs in routine clinical practice. If an association between polymorphisms and patients who do respond to drugs is found, then genetic status-dependent dosing and medication choice guidelines will need to be developed. To fully understand the impact these treatment decisions have, a randomized trial of gene-directed medication choice and dosing should be conducted. For metformin treatment of diabetes, for example, HMORN is conducting a case-control study of nonresponders to metformin versus responders as the controls. (In this case, metformin may interact with SNPs, or polymorphsisms, to affect the patient's response to therapy.) If the study reveals a strong association between polymorphism and response, then following assessment of clinical validity, an RCT would be conducted to study a gene-guided choice of metformin or sulfanyureas administered to participants tested for polymorphisms, versus standard of care for the control group. A second example is a case-control study of polymorphisms that influence patient response to asthma medications. Nonresponders to steroids, albuterol, and montelukast are being compared to responders in the control group. Again, if the study

reveals a strong association, following validation, an RCT would compare treatment with gene-directed choice of medication based on gene testing results to standard of care.

Barriers

Davis described several barriers to gathering data for decision making, including the current research infrastructure, inadequate data systems, and mismatched incentives for licensure. First, there is no formal research infrastructure with adequate funding for outcome studies of new genomic technologies. As a result, outcome studies have been "bootstrapped" onto discovery projects, meaning that the HMORN has had to be creative in obtaining the necessary resources to be able to conduct these studies.

Second, data systems are at least one generation behind. Most ICD-9 (International Classification of Diseases, 9th Revision) diagnostic codes and CPT (Current Procedural Terminology) service codes are inadequate to the task of efficiently identifying patients who have had their genetic status tested, and what the test results were. As a result, it is generally not possible to assess whether a genetic test (e.g., HER-2/neu oncotype) is being done appropriately, or whether treatment (Herceptin in the HER-2/neu example) is being used appropriately. The available observational data are inadequate for studies of test effectiveness, in part because the exposure is unknown. Without up-to-date data systems, RCTs of new genetic tests must be conducted instead, but these will be impractical to do in many circumstances.

Finally, Davis said, the decision to integrate a licensed genetic test into practice hinges on the demonstration of clearly improved outcomes in large population-based settings. For some tests (e.g., determining oncotype or predicting variations in warfarin metabolism), RCTs may be feasible and justifiable. For others, however, clinical trials are not feasible. Observational data may suffice, but may only be available post licensure. Regardless, Davis said, funding agencies are unlikely to provide support for evaluation of a commercial product post licensure, and there is no regulatory incentive for companies to conduct RCTs or observational studies post licensure. Without fundamental changes, Davis predicted there will be repeated examples of underuse of potentially valuable technology. He cited the example of the Amplichip CYP450 genotype test to predict phenotypic variation in metabolism of certain drugs. Although clinical validity was studied, clinical utility was not, and many healthcare organizations are not using this technology.

Davis concluded by reiterating that genetic tests, similar to pharmaceutical products, should be required to show proof of clinical utility and improved outcomes as a condition for licensure. That, he said, is "going to require a fundamental sea change in the way we think about genetic tests."

VETERANS HEALTH ADMINISTRATION

Sumitra Muralidhar, Ph.D.
Office of Research and Development, Veterans Health Administration

The U.S. Department of Veterans Affairs (VA) administers the largest health care system in the country, with 153 hospitals, 745 community-based outpatient clinics, and 245 veterans' centers that provide readjustment and mental health counseling to returning veterans. In fiscal year 2007, the VA treated 5.5 million unique patients. The VA uses an electronic medical record system and has a stable patient population, allowing for long-term follow-up. Most VA medical centers are affiliated with academic institutions, and serve as major training hospitals for clinicians. The three main divisions of the VA are the Veterans Benefits Administration, the Veterans Health Administration (VHA), and the National Cemetery Administration. The VHA has two branches, Patient Care Services and the Office of Research and Development (ORD). ORD has four services: (1) the Biomedical Laboratory, (2) Clinical Science, (3) Rehabilitation Research, and (**4**) Health Service Research. Within clinical science there is a cooperative studies program that launches large-scale, multisite trials within the VA system.

The Genomic Medicine Program

In 2006, the Secretary for the VA formally launched the Genomic Medicine Program to examine the potential of emerging genomic technologies to optimize care for veterans. As a first step, Muralidhar explained, a 13-member Genomic Medicine Program Advisory Committee (GMPAC) was established to help lay the groundwork for the program. (As a federal advisory committee, the GMPAC is subject to the Federal Advisory Committee Act.) Members of the committee come from the public and private sectors and from academia, and include leaders in the fields of genetic research, medical genetics, genomic technology, health information technology, health care delivery policy, and program administration, as well as legal counsel. There is also representation from a Veterans Service Organization.

A primary goal of the Genomic Medicine Program is to try to enroll every veteran who walks into a VA hospital into the program. To succeed in this goal, a new physical and technological infrastructure needed to be built, incorporating health information technology, education for providers and patients, genetic counseling, and workforce development, as well as governance, policy, and ethics. This system would facilitate not only research, but also translation into patient care.

Challenges

A significant challenge for the program has been that the VA is a very large, operationally decentralized system. Even though there is a centralized electronic medical record system, the VA is divided into 22 regional areas. Each operates independently on its own budget, with variability in infrastructure, operations, and capabilities across the system. Another challenge is the ability to incorporate emerging needs of genetic and genomic information within the existing information technology infrastructure. Keeping up with rapidly evolving genomic technologies is also a challenge. Budget constraints are a concern, and building one program can take resources from another. Ultimately, the program cannot work unless veterans are willing to participate.

Addressing the participation concerns first, in 2007 the VA launched a consultation project to assess veterans' knowledge and attitudes about genomic medicine. This was facilitated through an interagency agreement with the National Human Genome Research Institute (NHGRI) and conducted under a cooperative agreement by the Genetics and Public Policy Center at Johns Hopkins University. The results of 10 focus groups in 5 locations across the country, and a follow-up survey of 931 participants, revealed overwhelming support among veterans for such a program. About 83 percent responded that the program should be undertaken, 71 percent said they would participate in the program if it was implemented, and 61 percent said they would be willing to go beyond basic participation. Examples included coming back for follow-up exams over time or allowing their medical records from non-VA health care to be added to the system (Kaufman et al., 2009). Interestingly, Muralidhar said, individual willingness to participate was associated with attitudes about research in general, attitudes about helping others and having a history of previous altruistic behavior, curiosity about genetics, and general satisfaction with the health care they were receiving at the VA.

Infrastructure Development

After assessing veterans' willingness to participate, the next steps were to determine what was available within the VA system; if the program should build in-house capability within the VA, or leverage infrastructure available at the affiliated universities or through contracts with industry, or some of each; and what the research agenda should be. As described above, the Cooperative Studies Program conducts large multisite clinical trials within the VA system, providing an infrastructure on which the Genomic Medicine Program could be built. Four clinical trials coordinating centers across the country administer the trials: four Epidemiology Research and

Informatics Centers, a health economics research center, a pharmacy coordinating center, and a central Institutional Review Board (IRB).

In addition, for the past 10 years or so, the VA has been banking samples from its clinical trials. A biorepository in Boston has about 30,000 blood samples and 6,000 DNA samples collected from various trials, and a capacity to bank 100,000 samples. The VA also has a DNA Coordinating Center in Palo Alto that links to the clinical information and patient data, and a tissue repository in Tucson that has a brain collection from amyotrophic lateral sclerosis (ALS) patients and tissue blocks. In 2008, the VA established a Pharmacogenomics Analysis Laboratory in Little Rock, which is now a Clinical Laboratory Improvements Amendments- (CLIA-) certified research genomics laboratory conducting large-scale genotyping. There is also a newly established Genomics Research Core at the VA medical center in San Antonio.

The information technology (IT) infrastructure also needed to be addressed. The VA has recently funded two IT projects, the Genomic Information System for Integrative Science (GenISIS) and the Veterans Informatics Information and Computing Infrastructure (VINCI). The GenISIS system is based in Boston along with the biorepository, the Clinical Trials Coordinating Center, and the Epidemiology Research and Informatics Center. Historically, research data, biological data, clinical data, and medical records have resided in separate compartments. Research is traditionally geared toward hypothesis testing, there is targeted data collection from individual studies, the data are used by a single "owner," and the work is discipline driven. In contrast, the goal of GenISIS is to move toward a comprehensive data collection and retention system that facilitates hypothesis generation, data analysis, repurposing or reuse of data, and interdisciplinary interaction (Figure 3-1). GenISIS allows for secure gathering, integration, and analysis of patient information; discovery research through shared expertise; repurposing of data for secondary analysis; validation of genomic medicine findings; and integration of those findings into clinical medicine. Thus, the short-term goal for GenISIS is to create and support a knowledge base that would facilitate independent research projects and collaborative repurposing of data. The vision for GenISIS for the longer term is focused on patient care, integrating clinical care and research activities for improved patient outcomes. The objective of VINCI is to integrate existing databases across the VA and create a secure, high-performance computing environment for researchers to access data.

Research Agenda

The VA research agenda is informed by the health care needs of veterans and, Muralidhar said, that approach would apply for genomics as

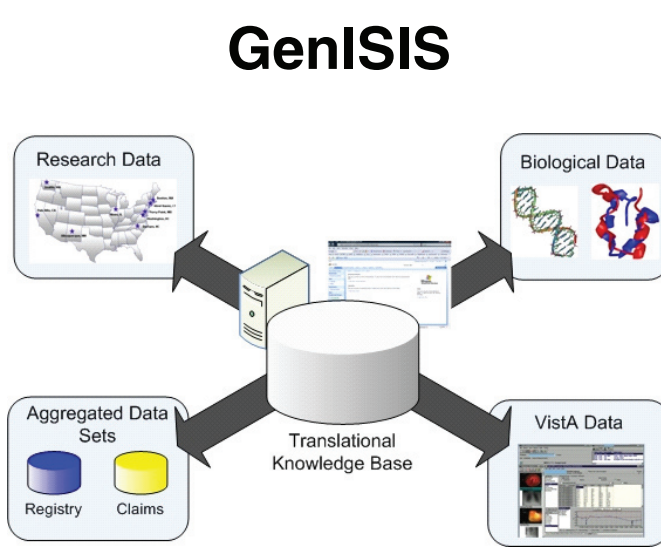

FIGURE 3-1 Integration of the components of the GenISIS system.
SOURCE: Muralidhar, 2009.

well. The GMPAC meets three times each year and advises the VA on the various emerging technologies and tests that are available to move into the clinic. There are specific scientific advisory and working groups, such as groups focused on hereditary nonpolyposis colorectal cancer or endocrine tumors, that make recommendations on algorithms that the VA could use for screening and testing. There is also investigator-initiated research.

Genomics research projects include: a genome-wide associate study of ALS, using the VA registry containing more than 2,000 ALS patients; a study of the genetics of posttraumatic stress disorder (PTSD) and co-morbidities, including 5,000 returning Operation Iraqi Freedom and Operation Enduring Freedom veterans with PTSD; and a serious mental illness cohort, with plans under review to recruit 9,000 patients with schizophrenia and 9,000 with bipolar disorder and a 20,000-reference cohort. Future research areas of interest to the VA include diabetes and pharmacogenomics. The VA also funds investigator-initiated projects focused on the genetics and genomics of chronic diseases.

Moving Forward

The biggest challenge going forward, Muralidhar said, is launching an integrated system to facilitate genomics research, as well as translation of that research to clinical care of veterans, in a system as large as the VA. The VA must also develop governance and policy for various issues, such as access to samples and data. Interoperability with external health systems will also be a challenge. Many veterans who obtain health care at the VA obtain all their care primarily from the VA, but some veterans also receive care from outside the system, and it will be important for the VA to consider those data as well.

Several education initiatives are under way, including working with the National Coalition for Health Professional Education in Genetics to implement a web-based tool to provide continuing medical education accreditation and point-of-care materials for clinicians and other health professionals. The VA also interacts, discusses, and actively participates with various other genetics/genomics-focused organizations, including NHGRI, PGRN, the American Health Information Community, the federal working group on family history tool development, and the Institute of Medicine (IOM) Roundtable on Translating Genomic-Based Research for Health.

INTERMOUNTAIN HEALTHCARE

Marc S. Williams, M.D., F.A.A.P., F.A.C.M.G.
Intermountain Healthcare Clinical Genetics Institute

In the late 1800s, the Church of Jesus Christ of Latter-Day Saints (LDS) began opening hospitals and creating a health care system in the southwestern United States. In 1975, the church sold all of its health care properties to Intermountain Healthcare, a secular, not-for-profit entity. With more than 20 hospitals and more than 1,000 directly employed physicians caring for more than 1 million patients from Utah and southern Idaho every year, Intermountain Healthcare is now the largest health care system in Utah. It is also the only integrated health system in Utah, incorporating an insurance plan, outpatient and inpatient care, home care, pharmacy, hospice, and other services under one administrative roof.

Research Priorities

Intermountain Healthcare has been involved in research for quite some time. Intermountain began research into informatics in health care in the late 1950s. The Institute for Healthcare Delivery Research was established in 1986, focused on quality improvement in health care delivery. An academic medical faculty was established in the 1960s, providing for protected time to pursue academic activities even though Intermountain is not affiliated with an academic institution. There is also modest internal funding for research and programs through Intermountain's Deseret Foundation.

Despite the long history of research at Intermountain, there was no overall vision for research until about 2 years ago, Williams said. The recently developed research mission statement calls for "excellence in clinical and translational research resulting in improved clinical care within the Intermountain Healthcare system." The vision for research at Intermountain is to improve patient care and well-being for many; encourage expertise; effectively communicate accomplishments; be financially responsible; and ensure that research is effectively resourced, optimally efficient, and complies with all applicable rules and regulations. Research priorities include retaining focus in areas of traditional strengths (e.g., cardiovascular, pulmonary/critical care, and informatics); supporting clinicians who have good research ideas, regardless of therapeutic area; using research to better support clinical program goals and objectives; and establishing genetics and genomics as a research strength across all specialties.

The rationale for including genomics as a research priority, Williams said, was that genomics will impact care across many clinical areas in the future. Also, Intermountain's information system positions the organization to be able to make important contributions to research in genomics. But, Williams noted, Intermountain recognizes that it cannot succeed alone. Intermountain needs to combine its unique assets with partners in the academic, commercial, and public health sectors. In this regard, Intermountain recently completed a master research agreement with the University of Utah. The VINCI program described by Muralidhar involves the bioinformatics faculty at the University of Utah, many of whom are Intermountain Healthcare employees.

Genomics Research

Genomics research at Intermountain is ongoing within existing specialty areas. Cardiovascular medicine, for example, has a biorepository of more than 16,000 samples obtained at the time of catheterization, and has created a genealogy resource modeled after the Utah Population Database.

This allows them to construct a genealogy for a given patient, look for other members of that family with similar diagnoses of interest, and conduct targeted recruiting of participants for discovery studies. Cardiovascular medicine also has a small molecular laboratory dedicated to genome discovery research. The group has conducted pharmacogenomics-based research, such as a prospective controlled trial looking at pharmacogenomic dosing for warfarin (Anderson et al., 2007). In pulmonary/critical care, there has been a lot of interest in primary pulmonary hypertension associated with the BMPR2 gene, and in maternal–fetal medicine, there are ongoing studies of genetic factors for premature birth, in partnership with the University of Utah.

To establish the Clinical Genetics Institute, thought leaders at Intermountain convinced the overall leadership that if genetic medicine was not done properly, there would be a significant risk to the system. They proposed that a central core of experts working across the entire system be established. Strategic planning commenced in 2002, hiring began in 2004, and the Institute began operations in January 2005. The primary objective of the Institute is to move evidence-based genetic medicine into clinical practice. Meeting this objective will require novel mechanisms, Williams said, and the Institute is leveraging expertise in informatics and health care delivery research as it moves forward with implementation. The Institute is also committed to working with providers to understand their needs and workflow.

Research efforts focus on the ability to define and measure outcomes of interventions. The institute will communicate research results to a broad audience, and hopes to build processes that will work not only at Intermountain, but could potentially be disseminated to other organizations.

Although there are currently only three staff at the Clinical Genetics Institute, their range of expertise spans genetics, health care delivery, quality improvement, informatics, and technology assessment. There is a clear internal vision of program goals, and strong support from some individuals in the larger system. On the negative side, the Institute has no discretionary resources beyond its personnel; large capital projects within the organization are decreasing the resource pool for all researchers across the system; and as noted earlier, there has been no shared institutional vision until recently.

Because of the limited availability of resources, a key component of the Institute's research strategy is partnerships. The Institute seeks to identify quick wins and targets of opportunity. Research is aligned with clinical efforts wherever possible, and methods are consistent with the Intermountain core values.

Current Research Activities

Williams highlighted several recent and ongoing genome-based research activities at Intermountain. One effort involved developing a rapid ACCE[1] model for technology assessment of emerging genomic tests, reducing the assessment time from 12 to 18 months following the standard ACCE structure, to several months using the rapid protocol (Gudgeon et al., 2007). Family history is another area of interest, Williams said, because it captures data that genomics cannot, such as shared environment and exposures. There are no published papers, he noted, on how primary care physicians use the family history data they collect. As a result, Intermountain is preparing a paper on this topic. There is also a family history tool for the patient portal in development, and Intermountain will study how best to move information from a patient portal environment (which would be somewhat analogous to a personal health record) across the firewall into the electronic health record.

Another topic of research is the economics of genetic services. The pharmacogenomic warfarin dosing study described earlier also collected actual cost data from all of the patients randomized into the trial. Epidemiologic research is also under way using Intermountain clinical data, in combination with the Utah Population Database and the National Children's Study.

Several informatics research projects are under way. Intermountain has created point-of-care education resources in its electronic health record, allowing care providers to click on an information button and link directly to genetics reference information for the patient's condition, including gene testing. As discussed by Davis above, current coding systems are inadequate in terms of genetics, and Intermountain is working to develop an appropriate infrastructure for coding and messaging of cytogenetic results. Intermountain also has a partnership with researchers at Harvard to study electronic communication of genetic test results.

Intermountain is also conducting health services research, looking at, for example, patient satisfaction with traditional clinical genetic services, identification of genetic diseases using the Clinical Data Repository, and implementation of a tumor-based screening for Lynch syndrome.

Challenges

From an internal perspective, developing a unified vision of genomic research has been a primary task. Different research entities within Intermountain are at varied levels of maturity regarding genetics and genomics.

[1] ACCE is discussed by Teutsch in Chapter 2.

Adequate resources are a significant issue, including not just funding, but also personnel and laboratory facilities. Identification and establishment of equitable partnerships between Intermountain and other outside entities is challenging. There is also a tension between Intermountain's primary mission of clinical care and the relevance of research to that mission.

Externally, the vision and funding of translational research remains a challenge. Less than 3 percent of federal dollars are allocated to research that is beyond basic discovery. As a nontraditional research environment, Intermountain faces extra challenges in the competition for awards. Intermountain is working to define the role of health care delivery research, which is more of a "real-world" scenario, versus a tightly controlled, hypothesis-based research model. One criticism that Intermountain has received is that, due to the unique resources available at Intermountain, results of its research may not translate to other institutions or systems. The current environment, including health care delivery and reform efforts and economics, impacts Intermountain's initiatives as well.

The Future

Williams closed noting that he sees several reasons to be optimistic about the future. The recent Bush administration had an interest in personalized medicine and the implementation of electronic health records, and this focus appears likely to continue under the Obama administration. Funds are now available through the Centers for Disease Control and Prevention National Office of Public Health Genomics and AHRQ to support health services research that aligns with the Intermountain strategy. There is also the potential that more traditional sources of funding, such as the National Institutes of Health (NIH), will shift toward real-world clinical applications of genomics research. Clinical Translational Science Awards at the University of Utah emphasize partnerships between academic medical centers and private entities, and there is more interest in general about public–private partnerships to broker information.

DISCUSSION

Wylie Burke, M.D., Ph.D.
Moderator

Transforming Genomics: Perceptions and Practices

Burke opened the discussion session by asking the panelists to comment on the phrase "sea change," as Davis said in his presentation there is the need for "a sea change in the way we think about genetic tests."

Davis responded that three sea changes could be very helpful. The first, and perhaps most important, he said, relates to how new technology is evaluated. While it is inconceivable that a drug would come to market based on clinical validity, that is what happens for technologies such as MammoPrint and AmpliChip. When technology products are released, Davis said, studies of how they impact health outcomes should be conducted. The federal government is hesitant to fund outcome studies of technologies that have been developed by industry because they could potentially be used for marketing. A second sea change involves IRBs, which, much like clinical data systems, are a generation behind. IRBs still hold the opinion that patients don't want personalized medicine, that it is very risky, and that people are primarily concerned about privacy. Risk and privacy are valid concerns, Davis said, but we need to move away from viewing these studies as extraordinarily high-risk ventures, and think of them as part and parcel of the 21st-century medical enterprise. The third change needed involves funding. Davis cited recent funding announcements for studies of gene–environment interactions that do not pay for any specimen collection, only seeking to fund studies to be done using existing infrastructure or biobanks.

Williams said one thing that needs to change is that insurance companies are the *de facto* regulators of gene-based medicine. A second issue is that funding favors RCTs, and has not been supportive of real-world clinical trials and health services research. It takes years for something that is known to be effective to be put into practice, and unfortunately, it also takes years for something that is found to be ineffective to be removed from practice (unless there is a lawsuit, in which case removal from clinical practice can occur overnight). The third area where change is needed is coding. He cited a study done on Hereditary Hemorrhagic Telangiectasia (HHT) and juvenile polyposis (Williams and Wood, 2009), and the potential to use the Intermountain Clinical Data Repository to identify patients who may have undiagnosed HHT. Unfortunately, there is only an ICD-9 code for polyps, with no differentiation for an adenomatous polyp or a juvenile polyp. That limitation in coding nearly ended the study, Williams said, but

the group was able to capture the information from the pathology system. There also are no specific codes for any genetic tests that are in regular use. Updated coding systems are necessary to be able to mine data from information systems at the level required for genetic studies. Williams also noted that most economic models in use are based on public or national health system implementation, and called for the development of economic analyses that can be done at the level of the health care delivery system.

Muralidhar supported Williams' point about regulation. She said that at a recent Personalized Medicine Coalition meeting, participants raised the need for a separate agency to evaluate the effectiveness of emerging technologies. She added that a change in education is going to be necessary as well.

Teutsch said the process for insurance coverage is often a one-way stream. Once interventions are covered, "they're in," and if coverage is denied, "they're out." There is rarely the chance to revisit a coverage decision to determine if the intervention is being used effectively. Changing to a process of incremental implementation would allow for learning along the way. Generally, however, "coverage with evidence development" has only been applied for major, very expensive technologies.

A participant commented that the diagnostic tests used in cardiovascular medicine were adopted decades ago and became the standard of care, and now it is very difficult to study them to see whether they really have an impact on patient outcomes. The same paradigm may be occurring with genomics, he said, but the questions now being asked suggest to him that a sea change in thinking regarding technology assessment is beginning to occur. There is also a sea change occurring regarding attitudes toward funding of biomedical research. The current stimulus package includes an additional $10 billion in funding for NIH over the next 2 years, as well as $1.1 billion for comparative effectiveness research, specifically focusing on technologies already available to clinicians and for which efficacy has not been studied.

Database Issues

A participant asked Williams if the population of Utah is still as genetically homogeneous as it was when used in cohort studies, and how any changes in homogeneity would influence the Intermountain database. Williams responded that a recent study concluded that the heterogeneity within the Caucasian population in Utah is essentially indistinguishable from that of the United States and Northern Europe. African Americans are generally underrepresented in the Utah population, but Utah is not completely homogeneous. There has been an increase in the Hispanic population. Utah also has a unique population of South Pacific Islanders, most

likely as a result of the LDS Church's missionary efforts in Samoa, Tonga, and other island locales, and there is a Native American population that is representative of their founding groups within the larger population. From the perspective of the Genomewide Association Studies, however, the current population mixture is not going to be a significant factor.

A question was raised about the basic assumptions underlying the development of infrastructures and systems. A striking discovery, the participant said, is how many of the common polymorphisms associated with diseases identified through Genomewide Association Studies are actually just echoes of a much more detailed private polymorphism mix. Can the infrastructure that is being developed handle assessment of a single mutation in a family causing a disease? In addition, how much does *in silico* (i.e., computer-simulated) evidence count? How is environmental information going to be incorporated? We are not collecting any of the relevant information on the social environment, the built-in environment, or diet, she said.

Williams said that one way *in silico* modeling is useful in clinical practice is when an existing genetic test uncovers a "variant of unknown significance." From an individual counseling perspective, that type of information is extremely helpful. Standardization across testing laboratories for how to address new variants, such as additional tests to be run, and creating databases of mutations would be useful. *In silico* modeling is also helpful in terms of targeting direction or prioritization. To address environmental influences, Williams reiterated that Intermountain focuses on family history, and already has empiric data about several common diseases.

Teutsch said a major challenge for genomics is determining where to expend resources. The focus of the workshop is how to gather data, but another challenge is how to bridge genomics and personalized health data with public health and population health information. Otherwise, there could be a potentially costly one-on-one clinical approach that deals with individual risks, which may only be modest on a population basis.

Williams continued the point, asking which would have a greater impact on asthma: research on polymorphisms that predict beta agonist response, or environmental research to decrease the amount of particulates in the air? Most would argue that improving air quality would have orders-of-magnitude greater impact. But it is a much harder problem to solve.

The panel was asked how research initiatives would change if, or when, a widely available, affordable human genome with sequence-searching capabilities was available. Williams responded that it would completely change the paradigm of genetic testing. At a given price point, and at a given level of analytic validity, it does not make sense to pay a company thousands of dollars to search a specific genetic test if you could search the whole genome for $1,000, and then build database queries against those particular sequences. It would lower many of the barriers related to sample

collection and storage, and enhance access to information. It would, however, raise many questions about who would have access, and under what circumstances.

Medical Education and Practice

One participant commented that applicants to medical schools know how to conduct current technological procedures (e.g., gene splicing), but don't necessarily know why they are doing it. Williams responded that the percentage of doctors really interested in understanding why they are being told to conduct a specific test is relatively low. They are interested in managing their patients better, and have approached Clinical Decision Support to help them do that. For those who are interested, Intermountain's Clinical Decision Support System provides the ability to drill down through Intermountain's clinical guidelines, national clinical guidelines, and the basic literature, simply by successive mouse clicks within the electronic health record.

A participant noted that there may be upcoming revisions to the medical boards, combining parts one and two of the boards into a single exam encompassing both basic and clinical science. The participant said this transition time could be a window of opportunity to insert genetics back into the curriculum.

Another participant said that clinicians are often aware that a test exists and will request it, leaving pathologists caught in the middle between quality oversight and the lack of knowledge about the clinical outcomes of genome-based tests.

A concern was raised by a participant about professional societies promulgating guidelines that he said have no evidence basis. Fifteen years ago, for example, there was a burden of proof required before routine prenatal cystic fibrosis screening was adopted as a guideline. More recently, however, the American College of Medical Genetics recommended the adoption of spinal muscular atrophy screening for all U.S. couples, and he questioned where the feasibility studies were. How many millions of dollars worth of tests will be done before someone accepts the burden of proof and demonstrates whether there is clinical utility or not? Organizations need to make sure that recommendations are evidence based.

Davis added that RCTs simply cannot be done for all of these tests, or even the majority, but that does not preclude evaluation using other data sources. Vaccines, for example, are released and safety in large populations is followed for 5 years. These paradigms could be adopted for evaluating the clinical utility and safety of new genetic technologies.

Williams said professional organizations have a responsibility to scan the horizon, understand what the public is pushing for, and determine at

what point they need to intervene. He noted that for newborn screening, there are inconsistencies from state to state regarding which diseases are included in the screen. Williams said that professional societies need not refrain from taking any action until the data reaches a certain evidentiary bar, but they do have a responsibility to be absolutely transparent and explicit in terms of the evidence used to reach a decision.

A participant noted that there are concerns that by the time an outcomes study of a new technology is completed and disseminated, the technology is outdated and newer ones may already be in use.

Williams recalled that when he graduated from medical school, it was estimated that medical knowledge would double every 30 years. The doubling time of medical knowledge is now 7 years and decreasing. The whole continuum of education, from undergraduate, to medical education, to residency training, to practice, needs to be evaluated with an eye toward implementing rapid change as evidence develops.

Williams pointed out that issues surrounding reimbursement were not discussed. Reimbursement follows policies, not necessarily evidence. Barriers created by reimbursement practices are going to have a tremendous impact in terms of moving genetic tests into the clinic, especially if a test is ultimately defined as preventive.

Research Participation

A participant from industry noted that although panelists discussed the need for more RCTs and observational trials, the need for funding for sample collection, and problems in coding, biobanking, and other operational issues, these are the lesser problems from the industry perspective. Industry conducts RCTs and some observational trials, and adding the genetics component to them is a marginal cost. Companies are generally well funded, do not have to rely on the ICD-9 codes per se, and have good sample banking. The biggest obstacle, he said, is patient participation. A company may intend to collect DNA from 100 percent of individuals who participate in a subset of Phase I, and all Phase II-and-beyond clinical trials, but the participation rate is very low, and enrollment is challenging due to the imposition of a variety of obstacles and constraints by IRBs and Ethical Review Boards. A large trial must work across many of these review boards, which have different rules depending on the country in which they operate. What can be done to better facilitate enrollment and encourage patients to participate?

Teutsch noted that the Secretary's Advisory Committee has this constellation of issues on their agenda, and understands that Health Insurance Portability and Accountability Act (HIPAA) and IRB regulations need to be kept up to date with current ethical and legal needs and standards.

The committee plans to consider what could be done with those systems to facilitate research, while still protecting the rights and privileges of the individuals.

A participant drew attention to the recently released IOM report *Beyond the HIPAA Privacy Rule: Enhancing Privacy, Improving Health Through Research* (IOM, 2009). The committee, she said, called for an entirely new framework to address privacy issues in research. She also noted that the committee offered practical suggestions for changes that could be made based on interpretation of regulations, without necessarily drafting new laws.

Williams commented that many of the issues being discussed involve personal values as well as medical value. Genomic medicine, or personalized medicine, provides a real opportunity to learn from incorporating a shared medical decision-making model, ensuring that providers are not only delivering the best medical care, but providing care that patients highly value.

Data Sharing

An audience member questioned if the data in the various repositories was proprietary, or whether any researcher could, for example, use the VA data. She also wondered if the move towards comparative effectiveness research and electronic medical records would provide an opportunity to better leverage the information across all of these different systems. Could handwritten data in charts and pathology reports be entered into the electronic system, so that it could be used more easily to supplement the claims data?

Williams responded that researchers are welcome to use Intermountain's data in collaboration with Intermountain researchers. He also noted that in Utah, they have formed a genomic medicine workgroup that includes representatives from Intermountain, the University of Utah, Utah State University, the Salt Lake City VA Hospital, and a number of private groups. The group is in the early stages, but is looking to foster collaboration and find venues to disseminate information. Relating to information systems, he said, a project called FURTHeR (Federated Utah Research Translational Health e-Repository), which is being run out of University of Utah Biomedical Informatics, is examining ways to combine University of Utah health care data, Intermountain Healthcare data, and Salt Lake VA health care data into a larger dataset. The project first needs to address issues such as rules that govern use, deidentification, and security. Another issue is the lack of standardization across systems. Most aspects that are standardized do not relate to the types of information that are needed for genomics. There needs to be investment in the development of standards that can be incorporated into the next-generation information systems.

Muralidhar said that at the VA, the GenISIS and VINCI programs are working to electronically capture data from case report forms and various other handwritten materials. They are also considering ways to give researchers Internet-based access to the VA data.

4

Current Practices in Moving from Evidence to Decision

Panelists in this session were asked to address four questions: (1) What uses of genetics does your program consider? (2) What evidence do you need? (3) What kind of process is used to make the decision? (4) What infrastructure is needed to support the process?

RARE DISEASE MODEL

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The Evidence Review Workgroup provides timely information to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children to guide their recommendation decisions for adding conditions to uniform newborn screening panels. The workgroup is directly responsible to the Maternal and Child Health Bureau of the Health Resources and Services Administration, which staffs the Advisory Committee. The task is not to recommend specific screening tests, but rather to help the committee make decisions about whether to screen for a particular condition. The group is an interdisciplinary team of geneticists, state screeners, epidemiologists, consumers, and others, Perrin said.

To suggest a condition for consideration by the Secretary's Advisory

Committee for addition to the uniform screening panel, there is a nomination form on the Committee's website. Completed forms are sent to the Maternal and Child Health Bureau staff for technical review, then to the Advisory Committee for evidence review. The Advisory Committee may choose to send the nomination to the Evidence Review Workgroup to carry out a more in-depth evidence review for that particular condition. The workgroup then reports back through the Maternal and Child Health Bureau to the Advisory Committee, which then makes its recommendations to the Secretary of Health and Human Services.

The questions on the nomination form address the incidence, timing of clinical onset, and severity of the condition, as well as the modalities available for testing, clinical and laboratory validation of the test, confirmatory testing, and risks of screening and of treatment.

Evidence reviews for most of the conditions that are considered for newborn testing are impacted by issues of rarity, and therefore limited evidence, and issues of where the evidence may be. These conditions often affect one in 10,000 live births, but many conditions affect closer to one in 100,000, or one in 200,000 births. In most cases, there are no randomized controlled trials (RCTs) available, and correspondingly, data for review of effective treatments will typically come from comparative case series. The rarity of cases and the severity of most of these conditions make RCTs very unlikely in the future. There is limited information on costs and benefits across all potential outcomes (including true and false positives and negatives). Access to any evidence that does exist can also present a challenge. In the case of relatively rare diseases, there may be a moderate amount of unpublished data. There may be valuable data from Food and Drug Administration- (FDA-) regulated trials, and proprietary data from companies involved in producing treatments for particular childhood conditions.

Evidence Review Questions

When the Advisory Committee sends a condition to the Evidence Review Workgroup, the first step is to consider the rationale and the objective provided on the nomination form. Issues that are most critical are whether there are prospective pilot data regarding population-based assessments; whether the spectrum of disease is well characterized; whether there is a screening test capable of identifying the condition; and whether treatment is well described. The next step is reviewing any recent changes in treatment and/or screening.

To assess the evidence, the workgroup again reviews the condition and the test. The workgroup determines if the condition is well defined, what is known about the prevalence and incidence of the condition, and what is known about the natural history of the disease, including clinically impor-

tant phenotypic or genotypic variations. The methods and accuracy of the screening test are reviewed, including whether the test can adequately distinguish between early- and late-onset conditions. The workgroup also reviews information about the potential harms or risks of screening, cost of screening, cost effectiveness of screening, and pilot testing and experience that exists in the literature or is provided by investigators. Perrin noted although the workgroup asks these questions, in many circumstances the data are limited or nonexistent.

The next sets of questions move beyond the condition and the screening method to address confirmation of the diagnosis. The workgroup reviews the methods of diagnosis and the costs, both of diagnosis and of failure to diagnose the condition in a presymptomatic period. At the treatment level, the workgroup asks whether presymptomatic or early treatment improves outcomes, and what information exists about the benefits of treatment, both efficacy and effectiveness. Are the treatment options standardized or highly variable, are they readily available, and are they FDA approved? Again, potential harms or risks of treatment are reviewed, including existing evidence for false-positive screening results, or late-onset conditions. Finally, costs (of screening, diagnosis, treatment, late treatment, or failure to diagnose in the newborn period) are a main area of interest, but one for which in nearly all cases few data exist.

Evidence Review Methodology

As described above, the workgroup developed evidence questions, many of which apply broadly across conditions, although specific questions within a particular condition always arise, Perrin said. To answer the questions, the workgroup uses traditional methods, employing search engines to look for evidence from the past 20 years or so. The searches are supplemented by interviews with experts, including investigators studying the particular condition, and parents raising children with the condition. In some cases, Perrin said, investigators were willing to provide raw data and preliminary analyses. The workgroup, however, does not have the resources to conduct in-depth analyses of raw data. Special issues are also associated with the format of data and constraints on use. Whatever the workgroup produces for the use of the Advisory Committee becomes public record, which can be an issue for investigators who plan to publish the data they are sharing. Therefore, a clear agreement with investigators is needed that spells out what the workgroup is or is not allowed to share. Perrin noted that a number of medical journals seem willing to allow the workgroup to share a moderate amount of data with the Advisory Committee even though they know the data will be made public before publishing.

The workgroup has also developed conflict-of-interest policies that

apply to the workgroup staff, all consultants involved in the project, and anyone the workgroup talks with regarding a particular condition. Perrin noted that the process is similar to the bias and conflict-of-interest process that the Institute of Medicine uses for its committees, and goes beyond simple financial bias to understand other aspects that might influence a person's decisions.

The workgroup engages condition-specific consultants. Investigators experienced in a particular condition testify to the workgroup and provide data, but are not involved in the analyses or interpretation of those data. Consultants do review the workgroup's summary of their own work for accuracy, but do not review the interpretation of the data and do not have the opportunity to disagree with the workgroup's interpretation. They can, however, do that in a public fashion once the workgroup's data become publicly available to the Advisory Committee.

Systematic reviews generally focus on peer-reviewed, published literature (in English only). Review of "gray literature" (information not available through standard databases or indexes) is generally limited to unpublished studies and related data from pharmaceutical companies. Single case reports are excluded, but the workgroup has included case reports of four or six children. The workgroup uses traditional methods for data abstraction and quality assessment.

Results are provided in a format following the order and the content of the main questions listed above. Key findings are presented in summary and table form. The workgroup indicates where evidence is absent, and what information would be most critical for decision making. It is important to convey what is not known, and what the level of uncertainty is. Perrin reiterated that all decisions and recommendations are made by the Advisory Committee. The workgroup provides the evidence for them to make those decisions.

From the viewpoint of the advisory committee, the questions that tend to be most important are those related to incidence and prevalence of the condition of interest, and the effectiveness of treatment, especially early treatment, based on early identification. Other key questions involve the test itself:

- How does the newborn screening test work?
- What are the characteristics of the test?
- What is known about false negatives and positives?
- Can it distinguish between early- and late-onset populations?
- Are there population-based screening data to determine clinical validity?

The Evidence Review Workgroup is in the midst of its third review, which addresses Krabbe Disease, Perrin said. The first was Pompe Disease, which has now been reviewed by the Advisory Committee. The workgroup recently submitted its review of Severe Combined Immunodeficiency, which is under committee review.

DISCUSSION

Wylie Burke, M.D., Ph.D.
Moderator

Burke asked Perrin about the decision to establish the explicit and formal separation of the evidence review from the process of making recommendations, noting that other processes often do not do this. Perrin said the statutory authority rests with the Secretary's Advisory Committee, which was developed in response to the Children's Health Act of 2000. A participant added that the workgroup has no authority to make recommendations to the Secretary.

A participant suggested that the availability of treatment would play a major role as evidence for or against newborn screening. He asked what would happen if there was a treatment, but one that was not widely available, noting that the establishment of newborn screening would most likely result in greater availability of the treatment. Perrin responded that the workgroup struggled with how to gather evidence on treatment availability. Ultimately the workgroup deals with investigators working on the particular condition to understand what is known about the availability of treatment. He said that a condition for which there was no treatment would likely not pass the nomination process and would not reach the workgroup for review.

Another participant said a fair number of the screening tests already being done have no standard treatment, and asked when the workgroup would review them. Perrin responded that the workgroup reviews whatever is assigned them by the Advisory Committee. He noted that there are 29 conditions in the uniform screening panel recommended by the Advisory Committee in 2005, and whether some of those should be reexamined is a good question. The participant suggested that updates may be required by the National Guideline Clearinghouse.

DUKE GUIDED GENOMIC STUDIES

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Moving biomarkers from bench to bedside is a complex process. Although Figure 4-1 depicts the translation continuum as linear, a biomarker could follow myriad pathways, resulting in wide variation in the time it takes from discovery to clinical adoption. The Onco*type*DX 21-gene assay, for example, took approximately 8 years to make the journey from discovery to use by clinicians for predicting prognosis in breast cancer patients. Contrast that with C-reactive protein, Ginsburg said, which was discovered in the 1930s and is now making its way into clinical practice as a result of recent clinical trials.

Ginsburg and Califf (2008) recently published recommendations for organizational changes that could enhance modern clinical epidemiology. Ginsburg said many of those recommendations could also apply to the translation of genome-based technologies. Such changes would include the establishment of coordinated, perhaps centralized, biobanks with standards both for sample handling and informatics; the aggregation of genomic technologies into core facilities accessible to investigators; the development of interoperable informatics systems, including electronic health records and molecular, clinical, and imaging data; increasing the cadre of skilled biostatisticians and improving physician training in quantitative skills; and better

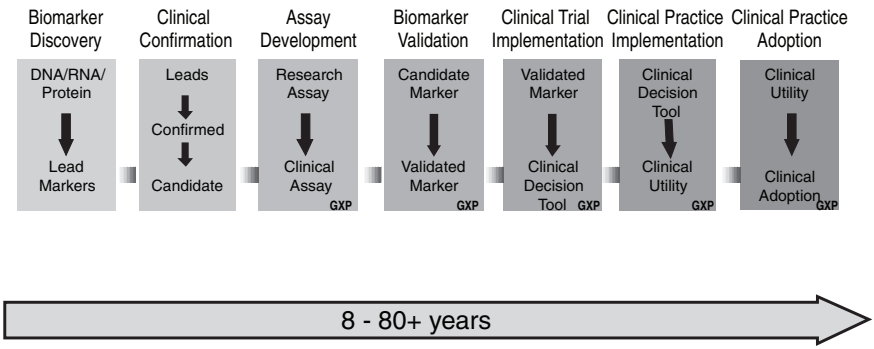

FIGURE 4-1 The translational continuum for biomarkers.
SOURCE: Ginsburg and McCarthy, 2001.

research and training in clinical decision making to understand the biological, psychological, and social aspects that go into making decisions.

Genome-Guided Clinical Trials

How can the evidence necessary for clinical adoption of genome-based diagnostics be obtained, Ginsburg asked, and how can this be implemented in health systems? Prospective genome-guided clinical trials are one means to develop the evidence required for clinical adoption. A prototype for such clinical utility studies is to consider areas where the current standard of practice is a choice between two or more therapies or combinations of therapies, where based on the clinical data there is clinical equipoise. In these cases, the question is whether genomic or genetic information informs the choice of therapy A versus therapy B, and leads to improved health and economic outcomes over random selection of care. A prospective clinical trial that asks whether a genome-guided approach to inform the choice between therapy A and therapy B could more clearly establish the clinical validity and utility of gene- and genome-based tests.

As an example, Ginsburg cited an effort to define a metagene that could predict recurrence in individuals with early-stage lung cancer (Potti et al., 2006). Using retrospective samples, a complex genomic (RNA expression) signature was established that can differentiate between individuals at high versus low risk for recurrence. Validation using several retrospective datasets showed approximately 85 to 90 percent accuracy of the predictive signature. Duke, in collaboration with the Cancer Therapy Evaluation Program and the National Cancer Institute, is now conducting a randomized, prospective Phase III trial of 1,500 patients with early-stage, non-small-cell lung cancer in the United States and Canada. In this trial, patients will have surgical resection of their tumor, and gene expression analysis will be conducted using the predictor. Following surgery, individuals predicted to be at low risk will continue under observation, which is the standard of care. Individuals predicted to be at high risk will be randomized to either observation or adjuvant chemotherapy. This trial design will test whether the genomic assay is accurate in its risk predictions by comparing the low- versus the high-risk groups receiving observation. The trial will also study the clinical utility of the risk information, assessing whether chemotherapy applied to individuals identified as high risk actually improved survival.

In addition to this type of predictive prognosis model, Duke has developed a series of gene expression signatures that predict sensitivity and resistance to a series of commonly used cytotoxic chemotherapeutic agents, including docetaxel, Topotecan, Adriamycin, 5-FU, Taxol, and Cytoxan. Publicly available datasets were used to validate these signatures. These tumor-derived signatures could have a significant impact on care, guiding

the selection of commonly used, standard-of-care cytotoxic chemotherapeutic agents across a variety of tumors.

A prospective Phase II clinical trial on the treatment of breast cancer in the neoadjuvant setting was initiated in summer 2008. Approximately 270 patients with Stage II/III operable, HER2-negative breast cancer will be enrolled. Following biopsy, participants will be randomized to standard of care or genome-guided therapy. The trial's endpoint is pathological response at the time of surgical resection of the tumor following chemotherapy. In the genome-guided arm, patients predicted to have a high response rate to the combination of doxorubicin/cyclophosphamide (AC) will receive AC. Those predicted to have a high probability of responding to docetaxel/cyclophosphamide (TC) will receive TC. Patients with predicted low sensitivity to either regimen will be randomized to AC or TC. The study is powered on the presumption that a 40 percent response rate will be achieved in the individuals receiving genome-guided therapy. Again this is a situation where clinicians choose between two available and relatively equal standard-of-care regimens. The question here is whether a genome-guided treatment strategy can improve outcomes—in this case, pathological complete response.

Pharmaceutical companies developing novel therapeutics can play an important role in translation of genomic information by adopting genomic technologies as part of clinical development. Ginsburg cited an ongoing clinical trial being conducted by Duke and Eli Lilly on advanced-stage, non-small-cell lung cancer, for which the standard of care is a combination of cisplatin and gemcitabine. Individuals predicted to be sensitive to platinum-based therapies (including cisplatin) will receive the standard of care. Individuals predicted to be resistant to platinum-based therapies will be treated with pemetrexed and gemcitabine. This strategy would potentially move a second-line cytotoxic therapy (pemetrexed) to first-line use in platinum-resistant populations.

Another approach a drug development company can take is to *enrich* the patient population in a trial in a way that allows development of more "targeted therapies." Ginsburg described an upcoming two-stage trial of advanced-stage, refractory, non-small-cell lung cancer patients being undertaken by Duke and Bristol-Myers Squibb. In the first stage, all participants will receive dasatinib, an experimental therapy for non-small-cell lung cancer that inhibits the Src family of tyrosine kinases, and Src activity of tumors will be measured in all patients. When assessing gene expression signatures of Src pathway deregulation from the tumors of these patients, if deregulation of Src in patients is found to correlate with the response of those patients to the drug, then in the second stage of the trial, only individuals whose tumors display an Src pathway deregulation signature will

receive dasatinib. The remaining patients will receive the normal standard of care.

These examples show how integrating genomic signatures into Phase II or Phase III clinical trial designs could lead to the inclusion of the genome-based treatment approach and potentially result in the incorporation of genomic information into the label of the therapeutic product, facilitating translation into clinical use.

Enabling Genome-Based Research and Decision Making

To assist oncologists in making better treatment decisions, an individual profile could be derived from analysis of a sample of the patient's tumor. Duke is developing a prototype clinical decision tool to help physicians understand what combinations might provide the best outcomes for cancer patients. The profile could provide the probability of response to many commonly used cytotoxic chemotherapeutic agents, and the probability of deregulation of known oncogenic signaling pathways. Such a profile could be used to rationally select an optimal therapeutic regimen from within standard-of-care combinations.

To assist with execution of genome-guided clinical trials, Duke has developed a specialized Clinical Genomics Studies Unit that houses Clinical Operations and Project Management, as well as Clinical Genomics Clinical Research Coordinators (CRCs) and Clinical Genomics Technology groups. The CRCs are specially trained to develop genomic protocols, draft informed-consent forms, develop patient and physician educational materials, navigate tissue samples through the complex health system, and assist with communicating the risks identified on the basis of genomic profiles. The genomic technology groups address assay standardization, ensure compliance with the Clinical Laboratory Improvement Amendments, develop the bioinformatics and algorithms necessary to deliver genomic information to the clinical trial, and establish longitudinal genomics data and sample repositories.

Ginsburg offered a variety of approaches in addition to the prospective trials that were discussed that could further enable evaluation of genomic markers. It is important to consider the value and impact of patient registries (for both common and rare diseases) for longitudinal follow-up, sample collection, and establishing robust phenotypes. Electronic health records offer the opportunity for population studies. A cooperative group mechanism could be established to consider and develop prospective genetic and genomic clinical trials. Industry participation provides opportunities through public–private partnerships, and through the ability to collect samples during clinical development, especially as part of Phase III and postmarketing (Phase IV) trials. Developing a national virtual sample bio-

repository that is linked to research and clinical data would also enable genomic marker evaluation.

An emerging concept at Duke is the Genomic Testing Advisory Committee (GTAC). The mission of the GTAC is to promote the appropriate evidence-based use of genetic and genomic tests in day-to-day clinical practice within the Duke University Health System. The GTAC reports to the Executive Committee of the health system, and serves as a resource to the Pharmacy and Therapeutics Committee and the Clinical Laboratories Committee, which are responsible for developing and deploying genome-based tests in the Duke system. The general process the GTAC follows is to provide an overview of the clinical evidence, risk information, use, and cost associated with the technology; develop a briefing document around the ACCE[1] criteria; make recommendations regarding incorporation into practice; and make recommendations about what types of educational tools and clinical decision support will be necessary to deploy the technology.

A computerized physician order entry tool was recently deployed at Duke for the use of warfarin. It provides relevant clinical and biological data to allow for the medication's appropriate dosing. Physicians can order a genetic profile including the genes VKORC1 or CYO2C9 by checking the appropriate boxes. When the box is checked, a window pops up that provides further information about the evidence base and rationale for using these genetic tests in guiding dosing decisions. To really drive clinical adoption of potentially valuable genetic tests into the Duke system, this type of clinical decision support tool needs to be integrated into the computerized order entry process. At this time, GTAC is focusing primarily on pharmacogenetic tests, and tests that are included in the label of an FDA-approved drug.

Ginsburg summarized the strategy Duke has adopted to integrate genetic and genomic testing into clinical practice (Figure 4-2). In the discovery phase, Duke is encouraging investigators to focus their research objectives on clinical decisions, particularly in areas where there is clinical equipoise and uncertainty (i.e., where more than one standard of care exists and the choice is generally random), and where the impact on clinical care and economics may be significantly high. The translational phase focuses on developing prospective clinical studies that both validate and establish the clinical utility of genome-based tests. Trials incorporate the use of registries, and the analysis of both health and economic outcomes. The implementation phase involves assay and algorithm standardization, incorporation of educational tools into decision making, policy development, and establishment of public–private partnerships that can help commercialize and deliver a product. The strategy is supported by an enabling infrastructure

[1] ACCE is discussed by Teutsch in Chapter 2.

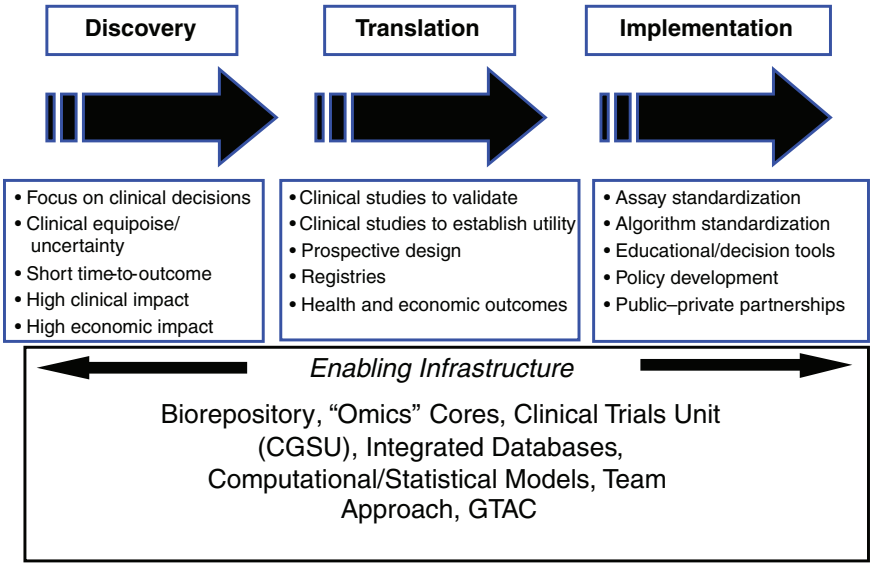

FIGURE 4-2 An integrated strategy for genomic medicine from bench to bedside. SOURCE: Ginsburg, 2009.

composed of biorepositories, integrated databases, genomics core facilities, a clinical trials unit, computational and statistical modeling, and the GTAC. Duke's strategy is a team approach that will help the health system understand which genome-based tests would be most useful to deploy in day-to-day health care practice.

NATIONAL CARDIOVASCULAR DISEASE REGISTRIES

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To demonstrate how genomics could be integrated into clinical practice, Brindis adapted a diagram by Califf et al. on the integration of quality into therapeutic development (Figure 4-3, adapted from Califf et al., 2002). Genomics can be incorporated at the concept stage. The concept leads to clinical trials, the results of which can be used to generate guidelines and performance indicators, after which the concept enters clinical use. Out-

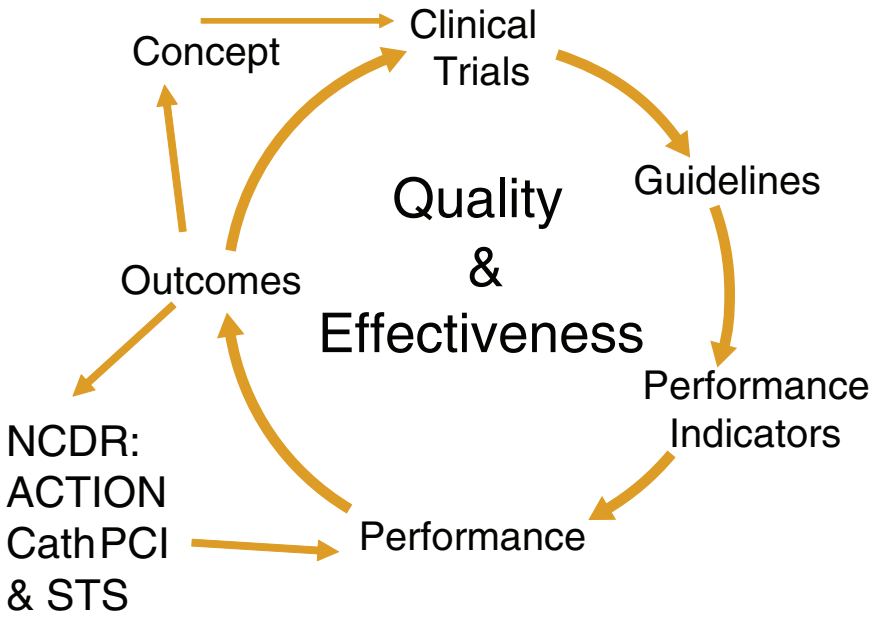

FIGURE 4-3 The cycle of clinical effectiveness.
SOURCE: Adapted from Califf et al., 2002.

comes of performance are collected in registries, such as the National Cardiovascular Data Registry (NCDR), which can provide feedback to enhance the quality of performance. In addition to improving quality at a local level, outcomes can lead to generation of new ideas and concepts, leading to new clinical trials, and the cycle continues. In this way, the outcome data can be used to improve both quality and effectiveness of care.

NCDR is a suite of hospital- and office-based registries and quality improvement programs focused on measuring outcomes and identifying gaps in the delivery of quality cardiovascular patient care. The mission of NCDR is to improve care, provide knowledge and tools, implement quality initiatives, and support research. There are now six components in the NCDR (CathPCI, ACTION-GWTG, ICD, CARE, and IMPACT registries, described below, and the IC3 quality improvement program), and two registry studies (the SPECT MPI study, looking at implementation of appropriate-use criteria for better stewardship of health care dollars, and an ICD [implantable cardioverter defibrillator] longitudinal registry).

The registry portfolio has multiple users and uses. The American College of Cardiology (ACC) uses it to conduct educational needs assessments, develop scientific insights, conduct research, and generate publications,

including clinical practice guidelines. Health plans have found it useful for developing participation requirements for preferred provider programs, and as a performance tracking tool. Researchers in academia, industry, and regulatory agencies are now actively using it for clinical research, outcomes research, and post marketing surveillance. Hospitals and physician practices use it for quality improvement, performance measurement reporting, and use review.

The structure of NCDR is such that each program has a steering committee, a quality improvement subcommittee, and a research and publications committee. Each component reports to the NCDR Management Board and the Clinical Quality Council, which in turn are responsible to the ACC board of trustees. To ensure the quality of data entered, NCDR uses online field checks for completeness and consistency, electronic data quality reports, and a national audit program where nurse abstractors perform annual onsite chart audits.

As a national registry, NCDR is striving to be patient focused, interoperable, transparent, and efficient, and to maintain high data quality. To be effective, it is necessary to have coordination of all the key players involved in health care, such as professional societies, hospital organizations, payers (Medicare and private), and federal institutes and agencies.

NCDR Registry Components

CathPCI was the first registry developed. It houses outcomes information on diagnostic catheterizations and percutaneous coronary interventions (PCIs). There are 1,100 hospitals participating, which Brindis said represents a market penetration of 70 percent of the nation's CathPCI hospitals. The registry incorporates nearly 9 million patient records, and 3 million PCI records. This robust databank has led to 30 published manuscripts, 4 in press, and 16 in preparation.

The ACTION Registry-GWTG is a registry for heart attacks, the result of a merger of the NCDR ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry and the American Heart Association Get With The Guidelines program. There are now nearly 400 hospitals participating, contributing more than 100 thousand patient records.

The ICD Registry is an ACC partnership with the Heart Rhythm Society and the Centers for Medicare & Medicaid Services (CMS) containing more than 330,000 patient records related to implantable cardioverter defibrillator implantation. An ICD longitudinal study is under way looking at different outcomes over time. The development of an atrial fibrillation ablation registry is under discussion as well.

The CARE Registry collects data on carotid artery revascularization and endarterectomy procedures. The IMPACT Registry (IMproving Pediat-

ric and Adult Congenital Treatment) is the newest registry. Initial efforts are focused on catheterization procedures, but eventually the initiative should expand into a national registry for congenital heart disease.

NCDR Data

The data NCDR provides to clinicians is usually in benchmark form, Brindis said. Practices can assess performance and look for opportunities for quality improvement. As an example, Brindis cited improvements in the timely administration of angioplasty following acute myocardial infarction (MI). The evidence-based care guidelines say that angioplasty should be done within 90 minutes after an MI. In 2004, only 38 percent of the procedures entered in the CathPCI registry had accomplished this. With that data feedback, and the application of quality improvement tools, more than 75 percent of procedures are now within guideline.

NCDR has developed a robust risk adjustment model that can be used to develop patient-centered consent forms that offer outcomes risk assessment based on the patient's clinical scenario to help the physician and patient make decisions. NCDR data are also being used to assess the safety and efficacy of performing angioplasty in facilities without onsite cardiac surgical facilities. As another example of the use of NCDR data, Brindis noted that the FDA approached NCDR regarding the safety of hemostasis devices used in cardiac catheterization, for which the published literature was very limited. Within a month, NCDR had 90 centers committed to submitting data to the registry on use of the devices. The data showed twice the level of complications associated with one type of device, compared to all of the others. The results were published and the device in question was removed from the market (Tavris et al., 2007).

NCDR Research

NCDR is a perfect platform for effectiveness and translational research, Brindis said. He expressed the hope that the federal economic stimulus package, with its support for research on comparative effectiveness, will acknowledge the role national registries can play in the diffusion of new technologies. NCDR can be used to inform public policy development on issues such as evidence-based reimbursement. There is growing interest in assessing patient quality-of-life and functional status. There is also significant interest in assessing efficiency and return on investment, linking registry health data with administrative data from CMS and health plans, for example.

Going forward, a key task for national registries is developing a longitudinal strategy for how to assess outcomes and incorporate genomics. To

do that, Brindis said, registries have to achieve data standardization and streamline data collection with electronic health records, decreasing the burden on hospitals. Other key elements include: evidence-based quality and performance measures; risk-adjusted outcomes, process, and structural measures; appropriateness and effectiveness measures; and financial data.

A national system of unique patient identifiers needs to be developed to fully realize the potential of collecting longitudinal data and evaluating outcomes, and relevant registries need to be linked. The goal is to convert procedural or episodic hospital-based registries into disease state patient-centered registries.

One NCDR effort under way with Yale University has merged hospital-based data from CathPCI with CMS claims data, looking at 30-day mortality after discharge for PCI. The challenge here is related to the lack of a unique patient identifier. Therefore the study has used probabilistic matching related to patient admission criteria.

In another effort, NCDR is merging CathPCI data with the Society of Thoracic Surgery database on coronary artery bypass grafts, looking at clinical outcomes for coronary disease, and perhaps identifying better clinical approaches related to patients with multivessel coronary disease.

NCDR and Genomics

A variety of issues need to be considered regarding use of NCDR to aid translation of genomic technologies. NCDR operates under a quality improvement model that does not require Institutional Review Board (IRB) approval or patient consent, Brindis said. But once NCDR undertakes the longitudinal work necessary for genomic-based research, it must implement IRB approval and patient consent processes and ensure compliance with the Health Insurance Portability and Accountability Act (HIPAA). There needs to be linkage with DNA banks and genomic and biomarker information. Brindis noted that a registry is not time limited like a clinical study, and issues of financial viability need to be considered. One funding model could be public–private partnerships with industry or biobanks.

NCDR is just beginning to think about the use of genetics in decision making, Brindis said. NCDR prioritizes all opportunities by considering the science, the political landscape, potential partners, the available operational resources, and the business case for undertaking the project. One way NCDR could participate in the translation of genomic technologies would be for professional societies and NCDR, in partnership with academic centers, analytical centers, health plans, and clinical research organizations, to work toward merging NCDR data with data from other registries and with payer data (e.g., administrative, pharmacy, and national death data).

DISCUSSION

Wylie Burke, M.D., Ph.D.
Moderator

Resources

A participant asked Brindis to elaborate on the public–private partnerships that NCDR has developed, specifically noting what the driver is for some organizations that are NCDR supporters.

Brindis said each registry has its own driver financially. CMS has been a partner for the ICD Registry because hospital participation is required for CMS reimbursement. This may not be a sustainable model, however, and NCDR is working to ensure there is a long-term viable strategy for the ICD Registry. Finding partners for postmarketing device surveillance is one approach. If CMS decides not to support the ICD Registry in terms of mandating participation, other payers, clinicians, and the FDA may find value in sustaining it long term. The CathPCI registry has no support from industry, Brindis noted, and each hospital pays about $3,000 to participate. An increasing number of states are mandating participation to oversee quality, particularly related to angioplasty at sites without onsite cardiac surgical facilities. For some other registries, the financial models are weak. Brindis noted that participation fees may be low, or no cost, but it is very costly for a hospital to enter the data, perhaps $100,000 or more. Even though NCDR may spend $20–$22 million to run the registries, the overall cost as a nation to participate is significant.

Burke noted that a theme throughout the day has been that resources are limited. She reiterated Ginsburg's point that randomized trials cannot be done for everything. Looking at different ways to maximize data collection is very important for creating the right combination of resources.

Brindis and Ginsburg agreed, and Ginsburg noted that the investment that the ACC and other participating organizations have made to build the NCDR infrastructure is phenomenal, and the data coming out of it are having a significant impact on medical practice. The question, he said, is how to take advantage of those resources for the evaluation of genome-based technologies.

Regulatory Issues

A participant asked whether pharmacogenetic assays were being developed as laboratory tests, rather than under an FDA Investigational Device

Exemption (IDE). What would the impact be if the research were conducted under an IDE?

The question of whether these tests might be subject to regulatory oversight is one of the uncertainties that still pervades the field, Ginsburg responded. A key question is understanding whether the test is considered high risk and will require a prospective clinical trial in order to prove its clinical value or clinical validity, or whether it is low risk and could be subject to a lower bar, such as a 510k submission (allowed to market by demonstrating substantial equivalence to a device that has been already cleared for marketing by the FDA). A major impact of having to go through the regulatory filing process would be the cost of conducting clinical trials of a greater breadth than is currently being done. Duke is very open to working with commercial firms, who generally have the resources to enable a true regulatory pathway for these tests. This is a major strength of public–private partnerships in these arenas, Ginsburg said. From the academic vantage point, the interest is in proving the value of the science on health outcomes, but to get to the next level and develop a test that is broadly available would require commercialization.

A participant from the FDA clarified that an IDE is an exception allowing for demonstration that the test is reasonably safe without having to demonstrate that it is effective. One usually seeks an IDE when there is a "significant risk." If test results are being used to select people for a particular treatment they would not otherwise receive, that presents a significant risk and should be done under an IDE, she said. It is a way to monitor the safety of a trial to ensure that people are not being exposed to more risk than they normally would have been.

Another participant commented on the use of algorithms for clinical decision support, pointing out that the FDA has expressed an opinion that some of these algorithms may be treated as devices and be subject to regulation. It will be important to understand the emerging regulatory environment related to genomic medicine because this could impact translation into practice, especially for complex genetic disorders where multiple polymorphisms impact expression of a phenotype or a response, and such algorithms could be used to aid decision making.

Data Quality and Use

A participant asked how, with multiple sources of input, NCDR protects its registries from the "Wikipedia phenomenon" or from the simple aggregate of error that may pollute the data. The sources that are inputting into the registry may, not deliberately but by error or ineptitude, submit data that are not good. The data are then part of the repository and become

"chart lore," where something becomes true because it is there. Is there uniform screening for entry of data?

Brindis responded that this is a real weakness of registry data versus data from RCTs. NCDR has completeness and quality checks, and an auditing strategy, but they are not perfect, he said. Some states are very robust in their auditing, such as Massachusetts, which uses NCDR as its platform, but then conducts extra audits with panels of clinicians reviewing coding. Data integrity is a valid concern. Registry data or observational data should not be overused to make decisions, he said. Registry data are just one part of the overall decision-making process.

Burke recalled Davis's point (see Chapter 3) regarding how the lack of specificity in ICD-9 codes for genetic tests significantly limits the usefulness of administrative data for research. She asked the panel to comment on limitations created by how data is recorded, and what registry data enable us to understand.

Brindis said the quality of registry data is much higher than the quality of administrative data, which he said has greater challenges in terms of accuracy, particularly related to co-morbid conditions and other clinical descriptors that would be important in the genomics field. He expressed hope that there will be good longitudinal registries, and reiterated the need for a unique patient identifier. He also noted the differences between data from RCTs and from patient data registries. The average patient age in the NCDR registries, for example, is 8 to 10 years older than those generally enrolled in RCTs. In addition, patients with co-morbidities are generally excluded from RCTs. This impacts the ability to develop evidence-based medicine for older patients or those with co-morbid conditions. Registries help add this information to the picture.

A question was asked about data on outcomes that are directly tagged to health, such as knowledge or satisfaction. Brindis said NCDR is just beginning to look at these areas. The first task is to look at quality of life and symptoms. In terms of patient satisfaction, large health plan organizations such as Kaiser have studied this, but NCDR has not addressed it.

Ginsburg said that in addition to clinical and economic outcomes, Duke is also looking at quality-of-life metrics in all of the studies being done. Separately, Duke has an employee-based program called Prospective Health, which uses traditional health risk assessment tools that relegate patients into higher or lower risk groups. The program is beginning to deploy some genetic testing for chronic disease conditions into that assessment. Also included are specific questions about workplace satisfaction, absenteeism, and overall satisfaction with the health program.

Genome-Guided Trials and Treatment

A participant asked about the Duke GTAC's decision process regarding implementation of the genomic testing associated with the physician orders for warfarin, noting that reports by the Evaluation of Genomic Applications in Practice and Prevention working group and Blue Cross Blue Shield concluded it was to soon to implement such testing for warfarin.

Duke is aware of the reports cited, and Ginsburg said they are inconclusive. Ginsburg responded that the GTAC was continuing to work on its methodology and that it would be using the warfarin case to develop additional data. For every thousand warfarin prescriptions that have been written since the FDA approved the inclusion of the test in the warfarin label, there have been only a handful of tests by the clinicians at Duke. He noted that there are several ongoing, prospective clinical trials that will hopefully establish more definitive evidence as to whether these tests should be done. The warfarin example should be viewed as a test case for how to develop a system to integrate genetic testing information and decision making into physician ordering. It is not necessarily focused on whether this test, in particular, would have an impact or not. The goal is to begin to understand the practice environment better so that issues can be addressed more directly when there are tests and other technologies ready for implementation that are going to have potentially more definitive impact on outcomes.

A participant asked how difficult it would be to export the Duke model to less academically focused institutions, particularly those overseas where many clinical trials are conducted.

Ginsburg responded that conducting genome-guided trials at just one site, Duke, has been a significant challenge. Yet Duke has overcome many of the hurdles and is developing the standards that would facilitate expansion of genome-guided clinical trials to other sites. The goal is certainly to establish an exportable model to a variety of settings (both academic and private practices) and to establish a network of private practices across the southeast and then nationally that would accelerate completion of the studies.

5

Panel: Where Are the Gaps?

Expanding on the previous panel presentations, three experts were asked to provide perspective on gaps in the systems for evaluation of genome-based technologies and health care.

BRUCE QUINN, M.D., PH.D., M.B.A.

Foley Hoag, LLP

Watson and Crick's 1952 article asserting that DNA was a double helix presented four or five different tracks of evidence, Quinn said. Isolated, any one of those tracks of evidence was insufficient to conclude that DNA was a double helix, but together, the combined evidence provided a clear case for their proposed structure. When talking about evidence-based medicine, there is always the discussion that more data are needed. The critical step, however, occurs in the human brain, which absorbs the data, makes judgments about it, and integrates it with other known information.

Most would agree, Quinn said, that the data have established that monoclonal antibodies which bind epidermal growth factor receptor (EGFR) will not inhibit tumor growth in patients whose tumors have a mutated KRAS gene. If the tumor does not have a KRAS mutation, then EGFR monoclonal therapy has a chance of being effective. One piece of information that is not always discussed, however, is that EGFR monoclo-

nal antibodies do not work very well overall, with 5, 10, maybe 15 percent of patients who have tumors with wild-type KRAS showing a response. Taking all the observations into account, it is generally agreed that a randomized controlled trial (RCT) to test the clinical utility of a KRAS gene test would not be appropriate.

There are also good basic science data on genetic variation in the response to tamoxifen or warfarin, but there is much more confusion about whether the genetics are clinically relevant. In warfarin management, for example, there are many additional considerations, such as height, weight, concomitant medications, diet, and compliance. In this case, RCTs would seem to be very important.

The way an Institutional Review Board (IRB) views a trial impacts whether an RCT is conducted. A study of the published literature found that RCTs that have gone through IRB review have a 40 to 60 percent success rate for the hypothesis being tested in the trial (Djulbegovic and Bercu, 2002). If there was a 10 percent chance of success, no one would fund the trial and an IRB would not approve it. Similarly, if there was 90 percent chance of success, the same thing would occur. A trial needs to fall somewhere in this 40–50–60 percent range to garner IRB approval.

Something that happens fairly often with diagnostic tests is that the 40 to 60 percent success range is already exceeded based on known information. For a genetic test, retrospective data may suggest an 80 or 90 percent likelihood of a particular result. Already, the predicted success rate of the hypothesis is outside of that 40–60 percent range where, based on documentation, an IRB will tend to approve it. An insurer, or another decision maker, may want to see data from an RCT, but the type of trials they are asking for would not likely be approved by an IRB.

It is important for companies bringing a diagnostic test into the marketplace, or facing insurer decisions, to remember that a product faces very different value propositions across its life cycle, Quinn said. In the early investment phase, intellectual property, barriers to competition, and development risk are important considerations. When seeking regulatory approval, meeting Food and Drug Administration (FDA) standards for safety and efficacy are paramount. After approval, the focus is on demonstration of clinical utility and comparative effectiveness. Quinn recalled the studies described by Ginsburg (see Chapter 4) where patients whose gene expression profile predicted low risk were in a control (observation) group; however, if the gene profile predicted high risk, there was a control group as well as a therapy group. One problem with this approach, Quinn said, is that the genetic test is not being compared to something else. True, the results of the genetic test can help assign therapy, he said, but if the gene panel costs $400, and a $50 antibody to do the same thing exists but was

not part of the trial, that is a comparative question that an insurer would ask.

Once a test has been approved for insurer coverage, adoption in the marketplace becomes the focus. Based on his experience as an insurer medical director, Quinn said adoption is also driven by economics, whether there is a profit margin for the physician or the institution. If a test does not bring in a profit, it is unlikely to be adopted. If there is a $30 profit margin, it will probably be adopted fairly quickly. Adoption also depends on the patient perception of the benefit. If the patient sees no benefit, then compliance or acceptance will be poor.

With regard to medical education, the basic biology of genetics is not that complicated, Quinn said. But to teach about all of the actual genes involved would be a mountain of information. For example, six genes are involved in tamoxifen dynamics, and five alleles for each of the six genes. Quinn said the educational challenge is to impart the right concepts to the physicians at the right time, rather than strictly educating about basic concepts or the details of thousands of genes.

In reviewing the way technology advances outside of medicine, Quinn noted that advances in the technology itself is only one part of the adoption and benefit of the technology. Often there is a long rollout period to understand different uses of the technology. Global Positioning System (GPS) devices, for example, are far better now than they were 4 or 5 years ago, but not because anything about GPS technology has changed. The satellites have been in place for 10 or 20 years, but the way the interfaces work and how people use them has changed. A panel conducted in 1980 or 1985 would probably have concluded that personal computers were not useful or cost effective, and that people should not have personal computers. But technology stumbles forward, there is investment over time, and people learn how to use the technology better. There is a risk of killing programs prematurely, Quinn said, just as there is the risk of asking for things that are actually impossible.

There have been several generations of radiation therapies for prostate cancer over the last couple of decades, Quinn said. First was standard radiation, approximating fields where the prostate would be, then conformal radiation, which was somewhat more accurate, then a technology called Intensity Modulated Radiation Therapy (IMRT), which is still more accurate. Now there is proton beam radiotherapy, which some centers have aggressively put into practice for prostate cancer treatment, and still another technology called stereotactic radio beam therapy. None of those have come out with a lot of data. IMRT was adopted fairly quickly once the Current Procedural Terminology (CPT) code was assigned. But if implementation had been slowed down, it could have created a difficult situation—when a company spends $200 million to develop an IMRT

machine, it cannot then lay off the employees, mothball its equipment, and wait 10 years for outcomes data, Quinn said. How the process should work is not exactly clear, he said, but if RCTs were the standard required for technology advance, radiation therapy would still be given by laying a towel on the patient and placing a lump of radium on it. There would not be the somewhat messy, somewhat garbled lurching forward, which is the way technologies advance, whether they are automobiles, television sets, or medical technologies.

ALFRED O. BERG, M.D., M.P.H.

University of Washington

Evaluation of Genomic Applications in Practice and Prevention (EGAPP) is an initiative from the Centers for Disease Control and Prevention tasked with establishing an evidence-based process for assessing genetic tests. Berg highlighted recommendations that EGAPP has released to date regarding the use of four specific genetic tests (EGAPP, 2009).

The first review focused on CYP450 genetic testing related to the use of selective serotonin reuptake inhibitors for the treatment of depression. The EGAPP working group found insufficient evidence to support a recommendation and discouraged the routine use of CYP450 testing until further clinical trials are completed.

The next review involved UGT1A1 genotyping in patients with metastatic colorectal cancer and the use of irinotecan. Again, the working group found the evidence insufficient to recommend for or against genotyping as a way to predict adverse drug effects.

In its review of Lynch syndrome, EGAPP found sufficient evidence to recommend offering genetic testing for Lynch syndrome, but decided that the evidence was insufficient to recommend a specific genetic testing strategy. Several approaches could be taken, Berg said, and the evidence was not sufficient to favor one over another.

Finally, EGAPP reviewed breast cancer gene expression profiling and found insufficient evidence to make a recommendation for or against its use because it was not possible to assess the balance of benefits and harms of the proposed use of the test. EGAPP encouraged further development and evaluation of the technologies.

Berg offered this brief EGAPP activity summary not only to provide the Roundtable with the current working group findings, but also to point out a recurring theme—the conclusion that there is often "insufficient" evidence

to make recommendations. Most people now agree that more evidence on new technologies is needed.

To fill in the gaps in the systems for generating evidence, Berg highlighted three issues from the day's discussions, all related to funding. The first issue relates to funding and infrastructure. Several speakers discussed the importance of funding infrastructure for data collection, registries, sample banking, or other activities. The second issue is funding for the research itself. The right balance of public–private partnerships and public support needs to be implemented. Finally, it is important to continue to fund "thinking." One of the activities the Roundtable does well is to thoughtfully consider a variety of topics. Participants leave Roundtable workshops with a renewed sense of priorities.

Thinking of outcomes beyond morbidity and mortality is important. EGAPP is preparing a manuscript discussing various outcomes, including some not mentioned at the workshop, such as the value of information to family members. Issues of economic analysis and modeling need attention. A vast number of polymorphisms seem to be related with fairly modest relative risks to cardiovascular disease, diabetes, and other disorders. There are not likely to be RCTs to study these, but modeling could provide useful information.

Berg said that as a family physician, and not an expert in genetics, each patient in his office is basically a clinical trial with a single participant. He collates all of the information he can extract from the patient history and from biological samples, and works with the patient to develop a strategy that will have the largest predicted balance of benefits compared to harms. But unintended and unexpected consequences always arise.

The main question is not whether more comprehensive genetic information is going to advance medicine in 5 or 10 years, or even 50 or 100 years, but whether it ever can. The problem is that genetic knowledge increases the number of factors that must be brought to bear on each clinical encounter with the patient. The more factors there are, the less likely a physician will be able to find good comparators for the patient sitting in front of him or her and be able to make predictions about care. Genetic variation is infinite. Multiply that by the number of environmental factors, and the answer is that the number of useful comparators will always be near zero. Every patient is unique genetically and in his or her environmental experience. If individual whole-genome profiles become common, a real concern will be providing information that will help inform, not hinder, clinical practice. Significant harm could result from looking for correlations, and trying to characterize patients in ways that actually complicate their care. Berg urged continued funding for dialogue such as the Roundtable, to help set goals for where genetic testing should be 10, 15, 20 years into the future, adequately addressing what is possible versus what would be useful.

KATHRYN A. PHILLIPS, PH.D.

University of California–San Francisco, School of Pharmacy

The Center for Translational and Policy Research on Personalized Medicine (TRANSPERS) at the University of California–San Francisco (UCSF) was launched in late 2008, and is focused on evidence-based assessment of personalized medicine and health outcomes. Phillips highlighted four steps needed to close the evidence gaps for personalized medicine and genomic technologies (Phillips, 2008).

The first step is to document the gaps in knowledge about actual clinical practices. This is accomplished by data analysis and through forums that bring together different perspectives. UCSF has developed approaches to analyzing medical records and claims data to better understand what is happening in the real world. Economic analyses are also important. Second, documentation, procedures, and interpretation of genetic tests should be standardized. This would help improve communication between laboratories and clinicians. A third area, which Phillips noted was not covered during the workshop, is providing incentives to close gaps. Policies can be developed that encourage generation of the type of data needed. One example is a policy implemented by UnitedHealthcare that requires clinicians to submit documentation of a positive HER2 test with the first trastuzumab claim. Lastly, creative approaches need to be developed to build the evidence base. Phillips noted that a variety of creative approaches were discussed during the workshop, including better coding and public–private partnerships.

Private Payers

One area that was not addressed in any depth during the workshop is the role of private payers. The seven largest health plans in the United States represent 100 million patients. Reimbursement issues are a significant barrier to moving the field of genome-based medicine forward. TRANSPERS held roundtable discussions and board meetings with health plans to understand what kind of evidence they are seeking, how they make decisions, how they interpret the evidence, and what incentives could drive collection of the right kind of evidence so that payers can make appropriate decisions. Payers agreed that is important to address the evidence gaps and the generation of evidence. Many factors lead to gaps, and a variety of solutions can help to close those gaps. Some solutions that appear obvious may be infeasible; for example, there are some barriers to using genetic modifiers for CPT codes.

Phillips was surprised by how different the payers are, and how different their product coverage decisions can be. They all agree, however, that the biggest challenge is the lack of clinical outcomes data. To help address this, TRANSPERS is working on methods to link claims data and patient charts so that use and outcomes can be tracked.

Payers are interested in developing evidence frameworks, but one finding that has become clear, Phillips said, is that one framework cannot be applied across the board to all payers, or relative to all topics. In addition, clinical utility is not the only endpoint. Contextual factors must be considered, such as FDA approval, political pressure, or physician demand, and TRANSPERS is developing a taxonomy of evidence gaps.

Private payers bring an important perspective to the evidence debate, but better mechanisms are needed to facilitate their involvement. TRANSPERS offers one mechanism for payer input, but more are needed. In closing, Phillips said it is useful to consider how various stakeholders view evidence gaps, and it is important to work with the stakeholders on using their data.

DISCUSSION

Wylie Burke, M.D., Ph.D.
Moderator

Knowledge and Contemplation

A participant commented on how rapidly patients are admitted and discharged, noting that most of that limited time is consumed by doing something to patients to justify the admission and discharge. This leaves residents and medical students with no time to think because contemplation is not reimbursed. Medical schools require more and more subjects in less and less time, all of which are evaluated by written examinations. There is more focus on passing the standard exams, and less interest in thinking. Physicians and scientists need time to think about what they are doing. Otherwise, the participant said, medicine will be ruled by algorithms and practice, which is not good for science or for human care.

Berg concurred with the comment about medical education, but questioned whether medical knowledge is really increasing geometrically. Some of the EGAPP reports start with hundreds of articles to review and boil down to four or five of substance. The number of times that research is truly changing practice is very small. Many articles add important informa-

tion to a larger body of evidence on a topic, but Berg argued that evidence that changes practice is not actually increasing that fast.

Payers

A participant said that "coverage with evidence development" is essentially asking payers to begin funding research as part of their mission. Some research is funded through standard payment mechanisms. For example, children's oncology treatment is often done in the context of collecting data. But to move toward coverage with an evidence development model, the payer needs incentives to be involved, because the margin in most cases is fairly thin. The participant supported the TRANSPERS effort to develop a taxonomy of gaps, and agreed there is great variety in the methodologies that payers use for technology assessment. A menu of frameworks for how payers might approach this would be very helpful, as well as a repository of evidence cataloging the gaps.

Phillips responded that she sees industry as paying for the evidence development, rather than payers. In other words, payers would not cover a technology unless the evidence was produced.

Quinn noted that there could be occasions where the new therapy was the same price as an existing therapy, making it cost neutral to cover, and entering information into a disease registry could be a requirement of coverage.

A participant asked about the role of the Centers for Medicare & Medicaid Services (CMS) in the generation of evidence. Does the fact that most Medicare coverage is for those aged 65 years and over play a role in CMS's knowledge or understanding of genetic issues?

Quinn responded that the Medicare system basically has no policies regarding genetic testing. Medicare is considering whether or not to cover genetic testing related to warfarin. Many genetic health issues would be uncommon in Medicare's general population, but 10 percent of Medicare patients, or 4 million people, are under 65.

Phillips added that the popular thought is that private payers tend to follow Medicare decisions. But even Medicare is not a monolithic plan, and local and national coverage decisions can differ. Companies will sometimes seek a local decision that then preempts a national decision. Payers are all considering the same factors, but how they interpret those factors is where the variation occurs.

Technology Development

A participant said market behavior is one difference between health care technologies and technologies such as the personal computer. The

people who recognize and reap the benefits of personal computers, and the people who pay for them, are the same. Therefore, if the technology is good, it develops into a market. This is not the case in health care. Also, in the case of personal computers or similar technologies, the benefits are realized almost immediately. In the case of chronic diseases, the benefits may be realized many years later, or they may be imperceptible. For example, if the technology reduces the risk of developing a cancer from 10 to 5 percent, 90 percent of people would not normally benefit, and there is no way to know who the 5 percent who would benefit are. The beneficiaries are not paying for the technology. It is a different kind of market structure.

An audience member stressed the importance of the patient perspective in development and translation. For example, he said, a challenge to conducting RCTs comparing surgery versus radiation therapy was that patients were not willing to be randomized to a treatment group. They had clear preferences for either surgery or radiation therapy. Another example he offered was that it was patients who saw the positive impact of mammogram screening for breast cancer who lobbied Congress for prostate-specific antigen screening for prostate cancer.

A participant commented that companies should be thinking about prospective evaluations of medications during the development process, so that treatments come out with prospectively evaluated companion diagnostics.

Another participant said that technology should not be released without at least some system in place to study the outcomes. A system of prioritizing is needed to determine what needs to be studied by RCT and what can be studied by observational data. Medicine has a long history of new technologies, such as computerized tomography (CT) scans or mammography, coming out with compelling, intuitive information, which then makes it almost impossible to study via a classic RCT. These are the situations where it is absolutely necessary to study the impact of this technology on human health. Berg agreed, and said that as genetics research identifies more variables in the characteristics of individuals, it exponentially increases the size of randomized trials necessary to look for differences in outcome.

Are Genetic Tests Unique?

Panelists were asked whether the same standards that apply to all other aspects of medicine should apply to genetic tests, or if there is something special or different about genetic tests in terms of the need for evidence, the associated politics, or the public demand.

Quinn responded that in general, there is nothing special about genetic tests. Germ-line testing is perhaps a little different because it is conducted once in a lifetime. Berg agreed, with the exception of the impact genetic testing can have on family members of the patient. He cited the EGAPP analysis

of Lynch syndrome, where genetic testing was recommended because of the potential benefit to family members. The tests that one does in medical care otherwise generally do not have implications for family members. Burke said that from the clinical genetics perspective, the tests that tend to fall out as different are the ones with high predictive value, which are generally the ones for single-gene diseases.

International Collaboration

A participant stated that in the basic research arena, there has been significant international collaboration through the Genomewide Association Studies, which leveraged the different strengths of different nations. He asked the panel to comment on the extent to which international collaboration might be useful for translational research, noting that many other nations have complementary or more extensive registries, better electronic medical records, and single-payer systems.

Berg agreed and said colleagues in other countries are more likely to be able to deliver on promises of research because they have health care systems that make coverage decisions differently than the United States, and they may not implement practices until they have a certain level of evidence. Where the United States has struggled to conduct RCTs on prostate cancer, trials in Europe are proceeding well because they have enough patients who have not been screened to be able to conduct the studies. The health technology assessment programs in the United Kingdom and Australia are quite sophisticated, and Berg said there is much to be gained from international cooperation on issues of evidence, not only on straightforward issues such as screening, but also on some of the treatment questions that have been discussed.

Prostate Cancer Radiotherapy as a Translation Case Study

A participant from Blue Cross Blue Shield expanded on Quinn's example of prostate cancer radiotherapy. Escalation in cost with relatively limited evidence about the value proposition is of concern, she said. The move from conformal radiation to IMRT increased costs per case from about $10,000 to $40,000. The known advantage of IMRT is a slight decrease in incidence of proctitis. That is a huge cost impact for treatment of a common disease. Cost estimates for proton beam radiotherapy will be considerably higher. It is important to understand whether these procedures add value to the health care system, or create distortions, especially when 45 million people are uninsured. She added that there are also distortions in the delivery of care. When Massachusetts adopted universal coverage, they found they lacked primary care physicians. The participant said there is an overem-

phasis on intensity of care and specialties, and an erosion of the core of the health care system, the primary care physician.

Quinn agreed that there is not a great deal of evidence for the escalation in cost of radiotherapy, and noted that the radiation oncology association has not commented about the increased costs. The participant added that there has been no willingness on the part of the professional group to promote comparative trials among radiotherapies or in comparison to other therapy. There is almost a lock on the development of information, but the costs keep growing.

Berg commented that prostate cancer is a very instructive example. The U.S. Preventive Services Task Force continues to be skeptical about screening for prostate cancer, and actually advises against it at age 75. Nonetheless, Medicare implemented screening when former Senator Robert Dole developed prostate cancer, and members of Congress approved Medicare coverage of the screening test. There still is no RCT showing that radiation treatment at any stage of the disease provides any benefit. Only one RCT shows that radical prostatectomy increases survival. Yet despite the insufficient evidence base, screening continues on a large scale. The problems facing genetic testing are similar to problems elsewhere in the system. Policy decisions and coverage decisions are made not only in the absence of the evidence, but sometimes in defiance of the evidence. Prostate cancer is an interesting case study where some things have worked well, while others continue to be baffling.

A participant said that IMRT is the classic physician conundrum. Radiation therapists try to deliver a dose to the tumor, which can be done with a few crude beams. IMRT was really a physics algorithm that allowed outlining of exactly where the tumor was, facilitating delivery of a radiation dose to the tumor and delivering less to the normal tissues. It became hard for doctors to not use IMRT, and to keep irradiating normal structures at high doses when unnecessary. Genetics is different in many respects, but the field is evolving in a way that clinicians have to decide how to best treat their patient given a great deal of uncertainty. The equalizer is going to be computer technology, and the ability of the physician to obtain data, proper analyses, and proper consensus when they need them.

Another participant said more large-scale randomized trials of IMRT or proton beam therapy are not what is needed now. What is needed is a better basic genetic understanding of prostate cancer so that men could be stratified by risk, and determinations could be made about which patients do not need treatment.

An audience member added that when considering prostate cancer treatment, those framing the question failed to ask what would be the incremental benefit over doing nothing. They considered one therapy versus another. There were no differences among the therapies in terms of ben-

efit. The main difference was in terms of harms, and they were relatively modest.

Priorities for the Next 5 Years

A challenge for the Roundtable, a member said, is that genome-based health is such a diffuse and enormous field with broad stakeholder representation. He asked the panel what they thought should be priorities for translating genomics into health care for the next 5 years. What is the best investment of intellectual and tangible resources?

Berg said family physicians in primary care take all comers, and never know what will be behind the door. Having tests or innovations that can be applied in that setting is no different for a genetic test than for anything else. Many factors compete for the attention of clinicians right now. Although most would agree that it would be great to find opportunities to use genetic tests, so far in his practice, Berg did not know of anyone using a genetic test for a common clinical condition. To be a viable business model, the tests need to be applicable to common clinical scenarios. Like any other innovation, it would need to be fast enough and cheap enough, and have demonstrated improvement in clinical outcomes in order to be adopted into practice.

Phillips said the Roundtable has a unique opportunity to bring the many different perspectives together, and to look across issues in an objective way. More generally, personalizing medicine will continue to be of interest, whether through genetics, family history, or various other means. There is a push toward comparative effectiveness and toward maintaining quality while reducing cost. The Roundtable's priorities should be developed within that context of where the health care system is going overall.

6

Closing Remarks

In the final session, three Roundtable members summarized what they each took away as the key messages of the workshop, and their thoughts on next steps.

SHARON TERRY

Genetic Alliance

One of the problems in this society, Terry said, is dichotomist thinking: an optimistic or a pessimistic view; genetics versus other kinds of medicine; research versus clinical. In many cases it would be better to consider issues as continuums.

One theme of the day was whether the current research infrastructure is adequate to assess genomic innovation. On the other hand, questions were raised as to whether genomics is really different from other kinds of biomedical innovation. Are genetic innovations and genome-based health being layered on top of a broken health care system? Or perhaps the question is whether genomics or genetics can actually help fix what is known to be broken in the system. Can the same mistakes be avoided and inequities eliminated, or will genome-based medicine only compound the problems of the current health care system, particularly in terms of costs?

A task for the workshop was to consider what evidence is needed and

for whom. Teutsch showed how different stakeholders need different types of evidence for their respective decision-making processes (see Chapter 2, Figure 2-5). However, in doing this, Terry said, one must avoid dichotomies, or creating an "us against them" culture. Stakeholders must engage in crosstalk to understand where there are synergies or overlaps, and to develop continuums.

In closing, Terry said there is a great deal of stress in the system resulting from the difficulty of evidence development and assessment. A critical step is to develop novel partnerships to elucidate the value of genomics. Industry must work with academia, government, and consumers so that stakeholders understand their overlapping and disparate concerns, and then understand the investment each needs to make for post licensure studies, large cohort studies, registries and biobanks, and other activities that are needed to generate the evidence and address stakeholder concerns.

SHARON KARDIA, PH.D.

University of Michigan, School of Public Health

One goal of the workshop was to consider the integrated systems needed for evidence creation. The presentations demonstrated that these integrated systems are up and running in many ways. Some are just starting, some are more mature, and hopefully they will contribute to the development of a learning health care system. The evolution of genomics technologies is running parallel with the advance of other new innovations and, therefore, our systems needs to be adaptive. Kardia recalled Berg's comment that evidence-based research takes great care and infrastructure to conduct, and yet evidence that actually changes practice is rare. This is an important lesson, Kardia said. Although one strives to be efficient, effective, and streamlined to produce tangible results, as people, our processes are naturally messy. Even in that messiness, if one focuses on the common public good, pursues excellence in all arenas, and trusts in a collective process, then eventually progress will be made. In the past year, there has been progress in terms of the crosstalk among stakeholders, increased awareness of the key issues, and new ideas about how to translate genomics into improved health.

This is an adaptive process, Kardia concluded. There is a balance between doing and thinking. Are people spending enough time in that deeper thinking process, Kardia asked, to find the tipping points where things that seem so slow to catalyze can more quickly come to fruition? Currently, there is a sense of frustration in trying to figure out what to do

to speed up translation efforts. However, most people in this field are so focused on activities such as obtaining funding or creating stakeholder relationships that we lack a cognitive map of the complex issues. As a result, it is a very important charge for the Institute of Medicine Roundtable to spend more time thinking about and articulating this bigger view of the issues.

WYLIE BURKE, M.D., PH.D.

University of Washington

Throughout the day it was clear that funding matters for genomic translation, Burke concluded. Careful thought must be given to what is funded, with attention to funding both infrastructures and studies. Someone asked why some current guidelines are not evidence based. An alternative question could be: Why are there guidelines when there is no evidence? Guidelines exist because clinicians need to act. Therefore, careful consideration should be given to what information clinicians really need, and what new or different funding profiles may be needed to obtain that information.

Other discussion focused on Institutional Review Boards, the Health Insurance Portability and Accountability Act (HIPAA), and unique patient identifiers, showing the need for more crosstalk about those issues. The discussion also made clear that tone must be very realistic about what is achievable in terms of creating research infrastructure, and accepting that not everything can, or should, be tested by a randomized controlled trial. In funding research to acquire information for decision making, there is a need to determine what the right combination of evidence is. Thinking schematically or conceptually, what kinds of innovation need what kinds of evidence? What type of research infrastructures can produce meaningful evidence about what kinds of different applications?

Thinking ahead to where the technology is going is extremely important, Burke concluded. In research, as in clinical care, the cognitive piece tends to be underfunded. A priority-setting process is clearly needed. The Roundtable convenes many different stakeholders and, therefore, a Roundtable discussion about appropriate processes for priority setting would provide a forum for interaction on this topic among the different stakeholders.

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Appendix A

Workshop Agenda

Systems for Research and Evaluation for Translating Genome-Based Discoveries for Health

Beckman Center
100 Academy Drive
Irvine, CA 92612

February 12, 2009

Auditorium

9:00–9:15 am — *Welcome and Presentation of Workshop Objectives*
Wylie Burke, Chair
University of Washington

9:15–9:35 — *Generating Evidence for Decision Making: Does the Type of Decision Being Made Influence the Evidence Needed?*
Steven Teutsch
Los Angeles Public Health Department

9:35–11:45 Panel: Creating Evidence Systems

Each of the following speakers will address the following questions:

- What are your goals for genetic research?
- How do you decide what studies to pursue?
- What barriers did you overcome or still face?
- What do you see as the biggest research challenges going forward?

9:35–9:50	*HMO Research Network* Robert Davis Director of Research, Kaiser Permanente Georgia
9:50–10:05	*Veterans Administration* Sumitra Muralidhar Office of Research and Development
10:05–10:20	*InterMountain Health* Marc S. Williams Director, Clinical Genetics Institute
10:20–10:40	**BREAK**
10:40–11:45	Discussion
11:45 am–1:00 pm	**LUNCH**

1:00–2:45 Panel: Current Practices in Moving from Evidence to Decision

Each of the speakers will address the following questions:

- What uses of genetics does your program consider?
- What evidence do you need?
- What kind of process is used to make the decisions?
- What infrastructure is needed to support the process?

1:00–1:15	*Rare Disease Model* James Perrin Professor of Pediatrics, Harvard Medical School
1:15–1:35	Discussion
1:35–1:50	*Duke Guided Genomic Studies* Geoffrey Ginsburg Director, Center for Genomic Medicine

1:50–2:05	*National Cardiovascular Disease Registries* Ralph Brindis Regional Senior Advisor for Cardiovascular Diseases, Northern California Kaiser Permanente
2:05–2:45	Discussion
2:45–3:00	**BREAK**

3:00–3:30 Panel: Where Are the Gaps?

Three invited speakers will discuss their perspectives on the gaps in systems for evaluation of genome-based health care. Each participant will take 10 minutes to describe what he or she sees as gaps, given the day's presentations.

3:00–3:10	Bruce Quinn Senior Health Policy Specialist, Foley Hoag LLP
3:10–3:20	Al Berg University of Washington
3:20–3:30	Kathryn Phillips Professor, UCSF School of Pharmacy
3:30–4:15	Discussion
4:15–4:45	Brief Summary of What Was Presented and Next Steps Wylie Burke, Chair University of Washington Sharon Kardia University of Michigan Sharon Terry Genetic Alliance
4:45	**ADJOURN**

Appendix B

Speaker Biosketches

Wylie Burke, M.D., Ph.D. (*Chair*), is Professor and Chair of the Department of Medical History and Ethics at the University of Washington. Dr. Burke was a member of the Department of Medicine at the university from 1983 to 2000, where she served as Associate Director of the Internal Medicine Residency Program from 1988 to 1994 and as founding Director of the Women's Health Care Center from 1994 to 1999. She was appointed Chair of the Department of Medical History in 2000. She is also an Adjunct Professor of Medicine and Epidemiology and an associate member of the Fred Hutchinson Cancer Research Center. She was a visiting scientist at the Centers for Disease Control and Prevention (CDC) in 1998 and is a Fellow of the American College of Physicians. She has served on the National Institutes of Health (NIH) National Advisory Council for Human Genome Research and the Secretary's Advisory Committee on Genetic Testing. Dr. Burke's research addresses the social, ethical, and policy implications of genetic information, including genetic test evaluation, the development of practice standards for genetically based services, and genetics education for health professionals. She is also the director of the University of Washington Center for Genomics and Healthcare Equality, a Center of Excellence in Ethical, Legal, and Social Implications research funded by the National Human Genome Research Institute (NHGRI). 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.

Alfred O. Berg, M.D., M.P.H., has been at the University of Washington since 1977. Dr. Berg was elected to the Institute of Medicine (IOM) in 1996. In 2004 he received the Thomas W. Johnson Award for career contributions to family medicine education from the American Academy of Family Physicians, and in 2008 he received the F. Marian Bishop Leadership Award from the Society of Teachers of Family Medicine Foundation, recognizing his contribution to enhancing the academic credibility of family medicine. He has served on many national expert panels using evidence-based methods to develop clinical guidelines, including chair of the U.S. Preventive Services Task Force, co-chair of the otitis media panel convened by the then-Agency for Health Care Policy and Research, chair of the CDC Sexually Transmitted Diseases Treatment Guidelines panel, member of the American Medical Association/CDC panel producing Guidelines for Adolescent Preventive Services, member of the IOM's Immunization Safety Review Committee, and chair of the IOM's Committee on the Treatment of Post-Traumatic Stress Disorder. He currently chairs the CDC panel on Evaluation of Genomic Applications in Practice and Prevention, and the NIH State-of-the-Science Conference on Family History in Primary Care. He received his M.D. at Washington University in St. Louis and his M.P.H. at the University of Washington. He completed residencies in Family Medicine and in General Preventive Medicine and Public Health.

Ralph G. Brindis, M.D., M.P.H., FACC, FSCAI, is the Senior Adviser for Cardiovascular Disease for Northern California Kaiser and a Clinical Professor of Medicine at the University of California–San Francisco (UCSF). Dr. Brindis is a practicing interventional cardiologist with an active practice in consultative cardiology. His major interest in process measures and outcomes assessment in cardiovascular care has led to helping to create and implement various Cardiovascular Guidelines for Northern California Kaiser. Dr. Brindis currently serves as the Vice President of the American College of Cardiology (ACC). He has served previously as the ACC Governor of Northern California and as past president of the California Chapter of the ACC. Dr. Brindis is the current Chief Medical Officer and Chair of the ACC National Cardiovascular Data Registry Management Board, which oversees six cardiovascular national registries. He also chairs the ACC Appropriateness Oversight Task Force developing appropriateness criteria for noninvasive testing and coronary revascularization procedures in cardiovascular disease. He is the past chair of the ACC Quality Strategic Directions Committee. Dr. Brindis was the 2007 recipient of the national ACC Distinguished Fellow Award. He is also an active volunteer in the AHA. He has served on the California Affiliate Board and previously as President and member of the Board of the AHA San Francisco Division. He now serves on the Steering Committee of the national AHA Quality of Care and Outcomes

Conference. Dr. Brindis sits on the Cardiac Advisory Board of the State of California OSHPD initiative overseeing public reporting of hospital- and physician- specific coronary artery bypass graft (CABG) mortality. He also served on the National Blue Ribbon Advisory Committee for Cardiac Care for the Veterans Administration and currently serves on the VA Hospital National CABG Quality Oversight Committee. Dr. Brindis has more than 100 publications in national peer-reviewed cardiovascular journals. Dr. Brindis graduated from the Massachusetts Institute of Technology in 1970, then earned an M.P.H. from the University of California–Los Angeles (UCLA) in 1972. He earned his M.D. from Emory Medical School, *summa cum laude,* in 1977 with elected membership in Alpha Omega Alpha. His graduate medical training was performed at UCSF as a resident and chief resident in Internal Medicine and also as a Cardiology Fellow.

Robert L. Davis, M.D., M.P.H., is senior investigator and director of the Kaiser Permanente Georgia, Center for Health Research/Southeast (CHR/SE). He leads a team of investigators and staff in a portfolio of funded studies involving pharmacogenomics and pharmacoepidemiology, health services research, clinical trials of vaccines and pharmaceuticals, and prevention and epidemiology of chronic diseases. Dr. Davis's training included receiving his M.D. from the University of California–San Diego, a residency in pediatrics at Oregon Health Sciences University, and an M.P.H. in Epidemiology from the University of Washington. After earning his M.P.H. in 1993, he joined the faculties of both Epidemiology and Pediatrics at the University of Washington's Schools of Public Health and Medicine. After a sabbatical in 2004 with the CDC Office of Public Health Genetics, Dr. Davis became the Director of the CDC Immunization Safety Office. In 2007 became Director of CHR/SE in Atlanta, GA, where he currently focuses on genetics research in diagnosis and treatment. He collaborates with the HMO Research Network and the NIH-funded Pharmacogenomics Research Network in studies of human genetic variation and response to commonly used medication for diabetes and heart disease. Dr. Davis has published more than 110 articles and 8 book chapters, and serves as a reviewer for 14 journals.

Geoffrey Ginsburg, M.D., Ph.D., is Professor of Medicine and Director of the Center for Genomic Medicine. Previously, Dr. Ginsburg was with Millennium Pharmaceuticals in Cambridge, MA, where he was vice president of molecular and personalized medicine. At Millennium, Ginsburg was responsible for crafting strategy on the discovery of biomarkers, genetic characteristics that measure the effects or progress of a disease or condition and the use of those indicators for clinical prediction and diagnosis. Dr. Ginsburg developed and directed the preventive cardiology service at

Beth Israel Hospital in the late 1980s, and has served on the faculty of Harvard Medical School since 1990. In addition to his role in the Institute for Genomic Sciences and Policy, he is a member of the faculty in the Department of Medicine at Duke University Medical Center. Dr. Ginsburg received his M.D. and Ph.D. from Boston University. He completed his Clinical and Research Fellowships in Molecular Cardiology at Beth Israel Hospital and at Children's Hospital in Boston.

Sharon Kardia, Ph.D., is an Associate Professor of Epidemiology at the University of Michigan. She is Director of the Public Health Genetics Program, Co-Director of the Michigan Center for Genomics and Public Health, and Co-Director of the Life Sciences & Society Program housed in the University of Michigan School of Public Health. Dr. Kardia's main research interests are in the genomic epidemiology of cardiovascular disease and its risk factors. She is particularly interested in gene–environment and gene–gene interactions, and in modeling complex relationships between genetic variation, environmental variation, and risk of common chronic diseases. Her work also includes using gene expression and proteomic profiles for molecular classification of tumors and survival analysis in lung and ovarian cancers. As a part of her Center activity, Dr. Kardia is also actively working on moving genetics into chronic disease programs in state departments of health. Dr. Kardia was a member of three National Academy of Science Committees (Genomics and the Public's Health in the 21st Century; Assessing Interactions Among Social, Behavioral, and Genetic Factors and Health; and Applications of Toxicogenomics Technologies to Predictive Toxicology). Dr. Kardia received her Ph.D. in Human Genetics from the University of Michigan, was a Postdoctoral Fellow in the Department of Microbiology and Immunology, and continued postdoctoral work in the Department of Human Genetics.

Sumitra Muralidhar, Ph.D., is Scientific Program Manager for the Genomic Medicine Program in the Biomedical and Clinical Research and Development services of the Office of Research and Development, Department of Veterans Affairs. Since the formal establishment of a Genomic Medicine Program by the VA Secretary in 2006, she has been involved in establishing the framework for a genomics research program within the Office of Research and Development, including policy development, infrastructure development, and scientific review process development for genomics. She serves as the designated federal officer for the Genomic Medicine Program Advisory Committee, a FACA committee that advises the VA Secretary on the application of genomics to improve health care for veterans. Dr. Muralidhar coordinated an interagency agreement with NHGRI to conduct a survey of veterans assessing their attitudes, knowledge, and expectations

of a genomic medicine program. She is also currently coordinating a project with NCHPEG on the development of a web-based educational tool on heritable colorectal cancer for health professionals within and outside the VA. Her previous positions include Health and Science Adviser to the U.S. Senate Committee on Veterans Affairs; Scientific Program Manager for Infectious Diseases and Immune Disorders at the Medical Research Service, VA; Assistant Professor of Microbiology and Immunology at Georgetown University; and postdoctoral training at the National Institute of Allergy and Infectious Diseases and the National Cancer Institute. Her research focused on oncogenic herpesviruses, specifically the Kaposi's sarcoma virus. Dr. Muralidhar obtained her Master's in Genetics from Bangalore University, India, and her Ph.D. in Microbiology from the University of Maryland–College Park.

James M. Perrin, M.D., is Professor of pediatrics at Harvard Medical School and Director of the Division of General Pediatrics and the Massachusetts General Hospital (MGH) Center for Child and Adolescent Health Policy, a research and training center with an active fellowship program in general pediatrics. He is also Associate Chair of Pediatrics for Research at the Massachusetts General Hospital for Children. He chaired the American Academy of Pediatrics (AAP) Committee on Children with Disabilities and is past president of the Ambulatory Pediatric Association. For the AAP, he also co-chaired a committee to develop practice guidelines for attention deficit hyperactivity disorder and then a group advising the AAP on the implementation of the guidelines. His research has examined asthma, middle ear disease, children's hospitalization, health insurance, and childhood chronic illness and disabilities, with a recent emphasis on quality of life and use of primary and subspecialty care for children and adolescents with chronic illness. He currently heads the Clinical Coordinating Center (based at the MGH) for the national Autism Treatment Network. He also directs the Evidence Working Group reporting to the Maternal and Child Health Bureau for the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. Dr. Perrin was the founding editor of *Ambulatory Pediatrics*, the journal of the Academic Pediatric Association. Dr. Perrin has served on the IOM Committees on Maternal and Child Health Under Health Care Reform, Quality of Long-Term-Care Services in Home and Community-Based Settings, Enhancing Federal Healthcare Quality Programs, and Disability in America; the National Commission on Childhood Disability; and the Disability Policy Panel of the National Academy of Social Insurance (Chair, Children's Committee). He received a Robert Wood Johnson Foundation Investigator Award in Health Policy Research. He also served as a member of the Health Care Technology study section of the then-Agency for Health Care Policy and Research and

of the National Advisory Council for the Agency for Healthcare Research and Quality. A graduate of Harvard College and Case Western Reserve University School of Medicine, he had his residency and Fellowship training at the University of Rochester and has also been on the faculties of the University of Rochester and Vanderbilt University.

Kathryn A. Phillips, Ph.D., is Professor of Health Economics and Health Services Research and Director, Center for Translational and Policy Research on Personalized Medicine at UCSF. She holds appointments in the Department of Clinical Pharmacy, the Institute for Health Policy Studies, and the Comprehensive Cancer Center. Her research focuses on how health care is organized, delivered, and financed in the United States. She focuses on personalized medicine—targeting health care interventions to patients based on their genetics—and the impact of personalized medicine and targeted therapies on clinical care, health economics, and health policy. Her emphasis is on cancer screening and treatment. Dr. Phillips conducts cross disciplinary research across the basic, clinical, and social sciences and also across academia, industry, and government. She has served as an adviser to many government and industry groups as well as for start-up companies and venture capital firms. Dr. Phillips is Director of the UCSF Center on Translational and Policy Research on Personalized Medicine and leads an NIH research program on personalized medicine for colorectal and breast cancer as well as several foundation-funded studies on personalized medicine. She has published approximately 100 peer-reviewed articles in policy and clinical journals, including *JAMA*, *New England Journal of Medicine*, and *Health Affairs* and serves on the editorial board for four journals. Dr. Phillips holds degrees from the University of California–Berkeley, Harvard, and the University of Texas–Austin and spent 8 years working for the federal government in Texas and Washington, DC.

Bruce Quinn, M.D., Ph.D., M.B.A., formerly the Contractor Medical Director for the California Medicare Part B program, is a senior policy strategist within the firm's Government Strategies practice, where he focuses on Medicare coverage and payment matters for new technologies. He is a national leader in the areas of Medicare coverage and payment, claims and billing, and Medicare contractor reform processes. Dr. Quinn works with companies, providers, and venture capital investors to develop strategies for Medicare payment for new technologies. A large part of this work is on local and national coverage decisions. He focuses, in particular, on the emerging field of molecular diagnostics and personalized medicine. He also advises clients on Medicare Administrative Contractor reform and its effect on payment policy. Before running the Medicare Part B program, Dr. Quinn practiced in the Health & Life Sciences division of Accenture and was a

physician-scientist at Northwestern University School of Medicine, leading pathology research for Northwestern's NIH-funded Alzheimer Research Center. He also held academic positions at New York University School of Medicine and UCLA Center for Health Sciences.

Sharon Terry is President and Chief Executive Officer of the Genetic Alliance, a coalition of more than 600 disease-specific advocacy organizations working to increase capacity in these organizations and to leverage the voices of the millions of individuals and families affected by genetic conditions. She is the founding Executive Director of PXE International, a research advocacy organization for the genetic condition *pseudoxanthoma elasticum* (PXE). She is at the forefront of consumer participation in genetics research, services, and policy and serves as a member of many major governmental advisory committees on medical research, including the Food and Drug Administration Cellular, Tissue and Gene Therapies Advisory Committee and the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. She is a member of the Board of Directors of the Biotechnology Institute and on the Advisory Board of the Johns Hopkins Genetics and Public Policy Center funded by the Pew Charitable Trusts. She is the chair of the Coalition for Genetic Fairness, composed of advocates, healthcare providers, and industry working to enact effective federal policy to prohibit genetic information discrimination. She is also chair of the Social Issues Committee of American Society of Human Genetics. In 2005, she received an honorary doctorate from Iona College for her work in community engagement and haplotype mapping. Ms. Terry is a cofounder of the Genetic Alliance BioBank and serves as president of its board. It is a centralized biological and data (consent/clinical/environmental) repository catalyzing translational genomic research on rare genetic diseases. The BioBank works in partnership with academic and industrial collaborators to develop novel diagnostics and therapeutics to better understand and treat these diseases. Along with the other co inventors of the gene associated with PXE (ABCC6), she holds the patent for the invention. She co-directs a 19-lab research consortium and manages 52 offices worldwide for PXE International.

Steven Teutsch, M.D., Ph.D., is Chief Science Officer of the Los Angeles County Health Department. He recently retired from Merck & Co., Inc. In 1997 he joined the Outcomes Research and Management group, where he was responsible for scientific leadership in developing evidence-based clinical management programs, conducting outcomes research studies, and improving outcomes measurement to enhance quality of care. Prior to joining Merck he was Director of the Division of Prevention Research and Analytic Methods at CDC, where he was responsible for assessing the

effectiveness, safety, and the cost effectiveness of disease and injury prevention strategies. He has served as a member of that Task Force and the U.S. Preventive Services Task Force, which develops the *Guide to Clinical Preventive Services*. He currently chairs the Secretary's Advisory Committee on Genetics Health and Society, and serves on America's Health Information Community Personalized Health Care Workgroup, the Evaluation of Genomic Applications in Prevention and Practice (EGAPP) Workgroup, as well as IOM panels. Dr. Teutsch came to CDC in 1977, when he was assigned to the Parasitic Diseases Division and worked extensively on toxoplasmosis. He was then assigned to the Kidney Donor and subsequently the Kidney Disease Program. He joined the Epidemiology Program Office and became Director of the Division of Surveillance and Epidemiology, where he was responsible for CDC's disease monitoring activities. He became Chief of the Prevention Effectiveness Activity in 1992. Dr. Teutsch has published more than 150 articles and 6 books in a broad range of fields in epidemiology, including parasitic diseases, diabetes, technology assessment, health services research, and surveillance. He received his undergraduate degree in Biochemical Sciences at Harvard University in 1970, an M.P.H. in Epidemiology from the University of North Carolina School of Public Health in 1973, and his M.D. from Duke University School of Medicine in 1974.

Marc S. Williams, M.D., FAAP, FACMG, is an alumnus of the University of Wisconsin–Madison. He graduated with a B.S. in Chemistry in 1977 and an M.D. in 1981. He did a pediatric residency at the University of Utah. After 2 years of solo practice in Michigan, he joined the Riverside (CA) Medical Clinic as a general pediatrician and practiced there until 1991. From 1991 until joining Intermountain Healthcare, Dr. Williams was at the Gundersen Lutheran Medical Center in La Crosse, WI. Hired as a general pediatrician, he eventually pursued Fellowship training in Clinical Genetics, and was board certified in this specialty in 1996 and recertified in 2006. In 1999, he gave up general pediatric practice and became the Associate Medical Director of the Gundersen Lutheran Health Plan while maintaining his genetic practice. By combining these two areas of expertise, he developed an interest in the role of genetics in health care delivery. He has published and presented extensively on this topic. Since 2005, he has been the Director of the Intermountain Healthcare Clinical Genetics Institute in Salt Lake City, Utah. In addition to his administrative duties, Dr. Williams runs a clinic for evaluation of adults with mental retardation, birth defects, and genetic disorders. He is a Clinical Professor of Pediatrics in the Division of Medical Genetics and Adjunct Professor of Biomedical Informatics at the University of Utah. He is a director of the board of the American College of Medical Genetics, a participant in the Personalized Medicine Workgroup of the Department of Health and Human Services' American Health Information

Community Task Force, Vice Chair of the CDC's EGAPP Stakeholder's Group, a member of the CDC's CETT program review board, and a member of the Secretary's Advisory Committee for Genetics, Health and Society, having previously served on the Coverage and Reimbursement Task Force of that group. He is past chair of the Committee on the Economics of Genetic Services of the American College of Medical Genetics, as well as chair of the subcommittee on Health Care Systems of the Section on Genetics and Birth Defects of the AAP. He is Editor-in-Chief of the *Manual on Reimbursement for Medical Genetic Services*. He has authored more than 40 articles in the peer-review medical literature and has presented over 50 papers at national and international meetings.