

# EYES ON THE PRIZE: TRUTH TELLING ABOUT GENETIC TESTING

SUMMIT DATES: SEPTEMBER 20 & 21, 2007



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**Genetic Alliance**

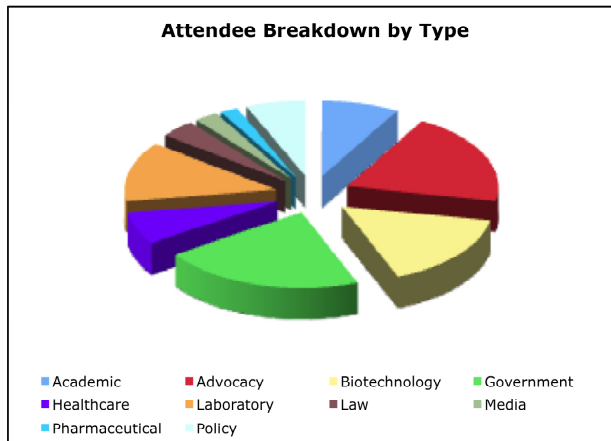
4301 Connecticut Ave., NW, Suite 404  
Washington, DC 20008

T: 202.966.5557 F: 202.966.8553

# Planning Committee

- **Joanne Armstrong**, Senior Medical Director, Aetna
- **Sherri Bale**, President & Clinical Director, GeneDx
- **Lynn Boyd**, Director, Public Health and Scientific Affairs, College of American Pathologists
- **Linda Bradley**, Geneticist, Office of Genomics and Disease Prevention, CDC
- **Kevin Conroy**, President & CEO, Third Wave Technologies
- **Greg Feero**, Senior Advisor, Genomic Medicine, National Human Genome Research Institute, NIH
- **David Feigal**, Senior VP, Global Regulatory Affairs and Global Safety Surveillance, Elan Pharmaceuticals; former Director, CDRH, FDA
- **Patricia Furlong**, Founding President & CEO, Parent Project Muscular Dystrophy
- **Jeff Gibbs**, Director, Hyman, Phelps & McNamara, P.C.
- **James C. Greenwood**, President & CEO, Biotechnology Industry Organization
- **Elliott Hillback**, Senior VP, Genzyme
- **Stuart Hogarth**, Research Associate, University of Cambridge
- **Kathy Hudson**, Director, Genetics and Public Policy Center
- **Katherine Johansen**, Scientist, Genetics and Molecular Medicine, American Medical Association
- **Michele Lloyd Puryear**, Chief, Genetic Services Branch, MCHB, HRSA
- **Alan Mertz, President**, American Clinical Laboratory Association
- **Robert Nussbaum**, Chief, Medical Genetics, UCSF School of Medicine
- **Paul Radensky**, Partner, McDermott Will & Emery
- **Michele Schoonmaker**, Director of Government Affairs, Cepheid
- **Randy Scott**, Chairman & CEO, Genomic Health, Inc
- **Sharon F. Terry**, President & CEO, Genetic Alliance

# Introduction



Individuals and families affected by genetic conditions, numbering in the millions all over the globe, suffer a great deal. While many do not yet label themselves as affected, we all carry dozens of deleterious mutations, many of which contribute to the myriad of common conditions from which we suffer. Although the human genome sequence was finished in 2000— seven years before this Summit—we are not at a point of regular translation of basic science to improved human health. We must accelerate the pace of

translation. To do this, we must understand the bottlenecks, discover the communication disconnects, and pave the way to increased collaboration leading to the discovery that is within our reach.

Genetic Alliance convened this Summit as ‘open space’; a place where all stakeholders could come and freely offer their concerns, opinions, and resources. We sought a safe place for truth telling, and we are grateful for the many stakeholders who rose to the occasion.

We welcome and support innovation, and know that we must be disruptive to create the new systems necessary to create tests, therapies, and treatments. We also know that the lay public needs to understand the options available to them, and people need assurance that these options are safe and effective. We are certain that an informed public, for whom decision-making takes place in an atmosphere of transparency, enhances access to services. The new age is not only one of new technologies, but also one of entry into a community commons, where it becomes increasingly apparent that creative use of shared resources in novel partnerships will promote the solutions we all seek.

This meeting is dedicated to those who depend on our good senses, and hope for the breakthroughs we imagine.

## Welcome & Context

Sharon Terry, President and CEO of Genetic Alliance, welcomed participants and set the tone for the two day Summit by reflecting upon its name, Eyes on the Prize: Truth Telling about Genetic Testing. The coveted prize is better health for all of us: for those we love as well as those we have never met, in the community, the country, and the world at large. Terry invited everyone to use the prize as a lens. While it is a challenge to abandon our individual agendas and conflicts of interest, doing so illuminates the path to real progress. Each sector of the genetic testing community—academia, advocacy, government, industry, clinicians, and patients—has a distinct perspective on the challenges and opportunities that accompany the path forward. However, that perspective too often translates into a narrow point of view.

By abandoning our turf and rising above our own perspectives, we can have dialogue about genetic testing that is more open, honest, comprehensive and fulfills our goal of “Truth Telling.”

Terry asked each panelist to declare all conflicts of interest, whether for profit or nonprofit, commercial or personal. Panelists disclosed their employers, pertinent financial holdings and board memberships, and any other relevant personal interests. This structure created an avenue for open, honest dialogue and gave listeners a more developed understanding of speakers’ perspectives. It also provided speakers with the opportunity to articulate and examine any biases before moving into the depth of the discussion. This helped all parties recognize questions that stem from self-interest, such as “What about MY disease? What about MY bottom line? What about MY institution’s interests? What about MY intellectual property?” The intent was not to eradicate self-interest, but instead to be transparent about it.

This led to productive questions that addressed the heart of what matters: “How can we improve the public’s health? How can we condense the timeline from research discovery to standard of care? How can we manage intellectual property and create a balance between sharing information through the public domain while maintaining financial incentives to support innovation?”

Terry laid out the goals of the Summit: to determine (1) consensus points within the genetic testing community, (2) hard questions that need further discussion, and (3) action steps.

## The Department of Health and Human Services and Personalized Healthcare

Greg Downing, PhD, Program Director for Personalized Healthcare for the U.S. Department of Health and Human Services (HHS), provided an update on HHS’s Personalized Healthcare Initiative, a high priority for HHS Secretary Michael Leavitt [note 1]. As defined by HHS, personalized healthcare consists of “medical practices that are targeted to individuals on the basis of their specific genetic code in order to provide a tailored approach.”

Downing emphasized that there are many factors involved in bringing new genomic technologies into the marketplace, and consideration of these factors is impacting the direction of HHS. There is “a systems problem in overall healthcare,” and HHS wants to transform the healthcare system so that it focuses on (1) prediction, (2) prevention, and (3) preemption. Ensuring that new technologies are accessible is of particular concern.

HHS thus seeks input from the community regarding analytical validity, clinical validity, and clinical utility. The Department is interested in the community’s needs within the current framework as well as projected future needs.

Downing mentioned ongoing federal efforts outside HHS. The Food and Drug Administration (FDA) recently released a new guidance on analyte specific reagents (ASRs). Also, the Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS) is working on a draft report that will provide more information on policies and practices for large genomic databases.

## HHS Goals

Even though no one can predict what medicine will be like a generation from now, we can lay the foundation for its advancement. To this end, HHS has established the following goals:

- Genomic information should be linked through public-private data partnerships. This would increase the ability to share data across research centers and other entities.
- Networks and policies should facilitate the collection of family history information and personalized health records. HHS recognizes that confidentiality, privacy and security issues need to be addressed.
- Genetic information must be used appropriately to prevent genetic discrimination in both the employment and insurance arenas. Testing and proficiency testing practices need a clear oversight scheme.
- Standardized access policies to federally funded databases of genetic information should be established. It is important for the public to understand the utility of these databases.

## Challenges

There are challenges to establishing personalized healthcare as the norm. Downing highlighted several. It is difficult to:

- ensure that the diagnostic arena has enough information to select the proper test
- evaluate value propositions and insure returns on investments
- manage both data overflows and deficits
- overcome health disparities and avoid the creation of new access hurdles

## HHS Personalized Healthcare Report

HHS released “Personalized Healthcare: Opportunities, Pathways, Resources” in September 2007. This report explains that in order to achieve personalized healthcare, there has to be an expansion of the scientific basis for health information technology. Layered over this foundation is the concept of intervention development and review. The result will be a greater utilization of pharmacogenomics and “more effective drugs aimed at narrower populations” [note 2].

These developments will then need to be integrated into clinical practice. Clinicians and patients must trust innovative drugs and diagnostics in order to adopt them. Therefore, both evidence and education can help streamline the adoption process.

Support for this pyramid of activity will culminate in the reality of personalized healthcare as an integral part of standard clinical practice.

# Survey of the Characteristics of a Range of Tests

Howard McLeod, PharmD, Director of the University of North Carolina (UNC) Institute for Pharmacogenomics and Individualized Therapy, examined the current state of genetic testing.

Medicine is moving toward the vision that Francis Collins, Director of the National Human Genome Research Institute (NHGRI), presented in 2003 [note 3]. Collins envisioned that each of us will eventually have our genetic sequence stored within an accessible medical record, and that we will have highly individualized preventative medical care. When we are in need of treatment, our decisions regarding medication type and dosage will be tailored to the individual.



Molecular diagnostics is a field that is rapidly growing and changing and leading us closer to Collins' vision. However, technology is evolving faster than the integration of genomics into medical practice.

The bottlenecks to progress are not all scientific. They include (1) the practices and habits of clinicians, (2) the costs associated with new tests, and (3) a lack of understanding about what these tests can and cannot do.

### Warfarin

McLeod presented information about warfarin, a very commonly prescribed blood thinner, as an example of a drug that is ideally suited to pharmacogenomics. The intent of pharmacogenomics is to take genetic information and use it to determine appropriate medication, including a safe and accurate dose. It is difficult for clinicians to determine the correct dose of warfarin for various patients because people metabolize the drug differently. If you give a patient too much of the medication, serious side effects can occur. If you prescribe too little, then the drug fails to prevent blood clots. Doctors have traditionally arrived at a steady dose by tweaking a patient's dosage based on observed responses to treatment.

Genetic testing can now be used to help determine proper dosage for individual patients. This type of testing greatly reduces the time to stable dosing. The FDA has approved updated labeling for warfarin that explains the importance of genetic data in prescribing the drug [note 4].

While tests like the one for warfarin certainly represent medical progress, it is important to keep the actual state of healthcare in mind. In a perfect world, physicians would always prescribe the correct dose from the start. Yet even with the genetic test for warfarin, this happens only 63% of the time. While this is a significant improvement over traditional prescribing methods (which yield a 9% initial success rate), there is still substantial room for refinement in the management of this drug.

### Genetic Constitution

It is essential for physicians to remember that DNA is only one factor to be considered when determining correct dosage. Age and body size are also important. In fact, it is vital for both the scientific community and the public to remember that genetic make-up is only one aspect of an individual's disease potential. There are many other contributing factors such as stress, exercise, and alcohol consumption.

### Trouble

McLeod described molecular testing as a field that focuses on "trouble." The first goal is to preempt trouble. This is an attempt to anticipate what the patient will face in the future. It is the reasoning behind newborn screening programs and the rationale for predicting breast cancer recurrence. It enables families to deal with the emotional aspects of disease and plan ahead.

The second goal is to understand a patient's current trouble. Treatments and strategies are developed to deal with symptoms. For example, tests are run to predict the likely origin of a tumor.

The third goal is to avoid trouble. Ideally, we will be able to use genetic markers to identify at-risk individuals and intervene prior to the development of disease. Overall, to deal with "trouble," we must develop tests to assess (1) risk of disease, (2) risk of side effects from medication, and (3) risk of lack of benefit from a particular medication.

Established methods of approaching single gene disorders have provided the basic infrastructure for the newer, more complex diagnostic tests. While genetic tests have only focused on mutations in a single gene that correlate with disease, genomic tests consider multiple gene interactions, gene expression, and sometimes the individual's genome. Many lessons have been learned and applied—for example, the value of genetic counseling is now well established.

According to McLeod, there are more formal evaluation frameworks for tests now than there were five years ago. The pathology community is serious about systematic reviews of testing. Nevertheless, “an unfortunate bit of craziness has occurred in the marketplace” with some direct-to-consumer (DTC) tests. McLeod suggested that additional industry-led certifications could provide the equivalent of a “Good Housekeeping Seal of Approval” and that this might be a better regulatory solution than additional legislation.

### **Patient Education**

At this point in time, other members of the medical team—not the patient—still primarily make treatment decisions. However, McLeod contended that patients:

- are very interested in their test results
- are capable of developing an understanding of complex diseases and tests
- desire details of their medical records
- do not usually retain long-term memory of the details of their medical records
- want to be part of the decision-making process

Government, academia, and practitioners need to better understand that information can be taken “all the way to the patient.”

In order to accomplish this information transfer, there is a great need for patient education tools. Patients need creative resources that are visually stimulating and accessible across the literacy stratum—for example, comic book formats are effective. Advocacy groups often provide the bridge between the medical community and their patients by creating literature that translates scientific information into a consumer-friendly format.

### **With Choice Comes Decision**

There are now multiple therapeutic options for most diseases, but “with choice comes decision.” It can be difficult to choose the correct therapy – patients exhibit wide response variations, and drug toxicity can be unpredictable. The cost of tests and therapies remains an issue, and therapy rationing is a reality. Both the payers and the patients factor cost into treatment decisions.

McLeod noted that disease prevalence is not the only consideration for allocating resources. Ethical, legal, and social issues (ELSI) must be taken into account, and rare situations merit research, too. He cited the severe drug reaction known as Stevens-Johnson Syndrome. Though a rare event, the syndrome's devastating effects make it a powerful example.

# Research and Development (R & D)

## Opportunities and Challenges

Medicine advances through continual research and development efforts. Both the government and private industry fund these efforts. This discussion brought together representatives from both sectors. The panelists were (1) Francis Collins, MD, PhD, Director, National Human Genome Institute (NHGRI), National Institutes of Health (NIH), (2) Randy Scott, PhD, President and CEO, Genomic Health, and (3) Brad Popovich, PhD, President and CEO, Sirius Genomics.

### **A Deluge of Discovery**

Collins opened the session with encouraging information: there has been a “deluge of discovery” with many origins. Advances in technology, along with endeavors such as the Human Genome Project and the International HapMap Project (a map of variations in the genome), played a role, as did the fact that large numbers of research centers have embraced the new technologies. These have all led to validated discoveries about the role that genetic variants play in determining an individual’s risk for common diseases.

Furthermore, the costs associated with discovery have been decreasing. Genotyping costs have dropped dramatically over the past four years. Today’s studies routinely have several thousand cases with several thousand controls; five years ago such a study would have cost billions of dollars. Today the cost has been reduced four orders of magnitude.

### **The Cancer Genome Atlas**

The Cancer Genome Atlas is a joint project of the National Cancer Institute (NCI) and NHGRI. Its purpose is to “accelerate our understanding of the molecular basis of cancer through the application of genome analysis technologies, including large-scale genome sequencing” [note 5]. This effort, which includes lung and ovarian cancers in its pilot phase, is expected to have profound consequences on the way that diagnostics are applied.

In the not-too-distant future detailed tumor signatures will be discernable. Collins predicted that these signatures would lead to additional diagnostic tests. Great progress is being made toward elucidating those genetic factors that play the most significant role in determining the risk for common diseases.

### **Intellectual Property**

NIH wants to ensure that data is appropriately placed in the public domain. However, access to the data is limited when restricted by intellectual property (IP) claims.

Collins described NIH’s intellectual property philosophy as follows: Early discoveries of associations between genetic factors and disease risk should be placed in the public domain and not claimed as IP. Claiming them as IP slows down the ability to apply these discoveries in the diagnostic arena because of patenting and licensing complications. NIH, however, is not anti-patent. It encourages IP claims on downstream applications (for example, the development of therapeutics or technology platforms).

### **Policy and Database Needs**

Some new policies are needed. The Genetic Information Nondiscrimination Act (GINA) is designed to protect individuals against discrimination based on their genetic information when it

comes to health insurance and employment. These protections are intended to encourage Americans to take advantage of genetic testing as part of their medical care [note 6]. As of this writing, GINA passed in the House of Representatives but has not yet been voted on by the Senate.

Companies that market genetic tests—both tests that are marketed to the consumer and tests that are marketed to physicians—should be required to deposit any available clinical validity or clinical utility data into a central database. This data should be kept updated and be made easily accessible to all interested parties.

Today, many tests are being marketed that have no clinical validity or clinical utility data. Establishing a requirement for a database would clearly identify which tests are making substantiated claims and which companies are engaged in “bogus marketing.” Collins quipped, “Sunshine is going to be the best disinfectant here.”

### **Biobanks**

Collins remarked that the United States would benefit from a project comparable to the United Kingdom’s Biobank. Such a project would enroll a large number of people in a national health study. Participants would be followed for many years, and every type of available information would be collected (for example, clinical information, genotypes, and environmental exposures). The data would then be correlated with disease incidence, thus furthering the study of disease. Unfortunately, Collins noted, the United States currently lacks both the will and the budget for a national biobank.

In addition to data on general genetics, disease, and health, better information about behavioral responses to the receipt of genetic information is needed. It cannot be assumed that patients and physicians will act upon evidence in a rational manner. A current project at Henry Ford Hospital offers healthy individuals the opportunity to be tested for eight different common conditions based on validated genotypes. Enrollees will be followed for a year in order to see what they do with the information. The study will answer the following questions: Were they able to comprehend the information? Does the information actually influence behavior?

### **The Computer Industry as a Model**

Scott presented an industry perspective on R & D. He noted that the end product of the genomics industry is actually information and suggested that it would behoove the healthcare industry to understand Metcalfe’s Law, which states that the utility of a network increases by the square of the number of users. Unfortunately, our healthcare system is not adequately networked. Even a healthy individual typically has several providers (dentist, gynecologist, family physician, etc.), among whom there is a negligible level of interaction and a lack of centralized records. A centralized database of medical records would improve care and the ability to track public health.

Pricing structure within the biotech industry has approximated the computer model of Moore’s Law, which describes the exponential rate at which the power of a computer can be doubled without increasing the manufacturing cost. Cost per unit of biological information has dropped steadily over time. In fact, DNA sequencing technology is actually advancing at a faster rate than Moore’s Law, which postulates that computer power will double every two years with little increase in cost.

Another parallel with the computer industry is the trend toward miniaturization. In the genomics industry, miniaturization has occurred in at least two areas: volume and price. The volume of material needed to perform a test declines over time. A test that used to require fifty microliters

of material now only requires five microliters. Similarly, just like the cost of a computer eventually dropped enough to create a market for personal computers, the cost of many genetic tests has now reached the consumer level.

Popovich contributed additional insights into the industry perspective on R & D. While cost and necessary sample volume are decreasing, barriers to commercialization persist. He used his company's work on sepsis as an example. There is only one approved drug for treating sepsis, but a genetic test might indicate that a patient's best therapy choice is an off-label drug. By definition, off-label drugs are not approved prescriptions, so physicians and patients face a dilemma, and providers often use off-label drugs in addition to the one approved therapy.

### **Industry Perspectives**

While technology continues to move forward, barriers to the utilization of the developed technology remain. Scott and Popovich enumerated some of those barriers:

- It takes years—if not decades—to move a test from discovery to standard clinical practice.
- Effective utilization requires changes in medical practice. Clinical data drives physicians to adopt products, and it is not feasible to produce clinical data for every test. As a society, we have to decide how much clinical evidence is sufficient.
- In some cases a company may develop a test that alters a practitioner's usual income stream. Practitioners might then resist change.
- In the ultimate hurdle, payers have to be convinced a test is worth the cost of reimbursement. Without reimbursement, it is difficult to achieve substantial adoption. Without a strong prospect of adoption, it is difficult to attract private investors.

Collins asked Scott and Popovich to comment on NIH's IP position that claims should only be allowed downstream. They explained that (1) competition is desirable because it encourages companies to improve their products; (2) the established business model of generic companies is to utilize the R & D foundation that was funded elsewhere; (3) if a genetic test provides adequate value and receives adequate reimbursement then the test is priced properly; and (4) there has to be some provision for IP claims and their economic return if the government expects industry to continue to invest in R & D.

### **World Health**

Audience questions and comments touched on the topic of world health. There are export barriers unique to genetic testing technology. Many developing countries lack basic technology such as refrigeration and a reliable supply of electricity. Without these basics, such countries are unable to utilize advanced genetic technologies. Indeed, some parts of the world remain desperate for the clean water and mosquito netting that would reduce their mortality rates. Nevertheless, the genetics community recognizes that (1) genetic testing can improve health across all populations, and (2) shortening the technology transfer time is a worthy goal.

### **Balancing Regulation and Innovation**

Panelists and Summit participants agreed that there needs to be a balance between protecting the public and allowing innovation to flourish. The marketplace is not regulating itself. Collins proposed a registry of genetic testing data, but questions remain. Who should maintain such a registry? Should it be the FDA? Or should it be an independent, nongovernmental organization?

# Translation and Test Development

The translational stage of genetic testing involves moving the technology from the research environment into the clinical laboratory environment.

A panel moderated by Christopher Austin, MD, Director, NIH Chemical Genomics Center, explored test translation and other elements of test development. The other three panelists were (1) Linda Bradley, PhD, FACMG, team lead, Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative, National Office of Public Health Genomics (NOPHG), Centers for Disease Control and Prevention (CDC), (2) Elda Railey, co-founder, Research Advocacy Network, and (3) Janet Warrington, PhD, Vice President, Standards and Government Policy, Affymetrix, Inc.

## **Analysis of the Translational Stage**

Austin described the translational stage as the hardest aspect of test development to manage. The research stage, which comes prior to test translation, and the clinical development stage, which comes after, both have more clearly defined parameters.

Bradley described three basic tenets of analytical validity:

- Does the test measure what it says it does?
- Through what method does the test detect its result?
- How well does the test detect results?

Once analytical validity is established for a genetic test, clinical utility must also be established. Clinical utility fundamentally determines whether or not a given test actually improves therapeutic options. This leads to questions about evidence: How much evidence is sufficient to prove test claims? There could be different standards for diagnostic and predictive tests. What should be done when the evidence is insufficient?

Bradley observed that personalized medicine and evidence-based medicine are not at odds with each other. Both can occur simultaneously. In fact, Warrington later noted that personalized medicine is not only in practice, but it is commonplace. For example, diabetic patients constantly monitor their blood glucose levels and tweak their treatments within a specific protocol.

Railey described the advocacy community as a bridge between the scientist and the survivor. She explained that advocates have been both innovative and creative. For example, the development of biorepositories by advocacy organizations (such as the Genetic Alliance BioBank) enables researchers to access samples and data that might otherwise be difficult to obtain.

Warrington pointed out that diagnostic tests have not provided the immediate gratification that is available in many other aspects of our culture. There are only a limited number of diagnostic products in development, and they are based on studies that began years ago.

She also noted that industry requires financial incentives to develop tests. Currently, tests that do not lead to treatment (for example, carrier screening for cystic fibrosis and Huntington's disease) are not generally reimbursed.

### Study Design

The panelists discussed proper resource allocation for medical studies. Money for studies is limited, yet there are many poor studies published. Why do poor studies continue to be funded? What changes in study design and approval can be proposed?

When a large drug company conducts a grossly expensive study and the study fails, is this a loss for everyone since those resources could have been placed elsewhere? Or is that scenario just a loss to the drug company's shareholders, employees, and subcontractors?

In order for a clinical research study to meet regulatory approval standards, there must be excellent communication between the entity that is conducting the study and the agency that is responsible for its approval.

Adaptive clinical trial design, which allows for changes based on interim results, is one approach, which recognizes that "evidence is a moving target." However, it is essential that the integrity of the collected data remains intact.

Austin asserted that "underpowered studies with marginal results that are not reproducible" should be avoided. Instead, researchers should learn from good studies. For example, studies proceed with fewer problems if the overseers and payers are consulted on the study design.

Unfortunately, there are incentives in the current system that drive production of the minimum publishable unit because such efforts offer rewards to the individual or the institution (for example, tenure or prestige), but this type of result provides no real benefit to public health.

Disease incidence and prevalence cannot be the sole criteria for resource allocation. Rare diseases also merit dollars and attention.

## Clinical Delivery/Commercialization Roundtable

This roundtable discussion illuminated the FDA test approval process. Robert Egge, Executive Director of the Alzheimer's Study Group at the Center for Health Transformation, moderated as the intellectual property management theme continued to percolate. The other panelists were (1) Steve Ferguson, MBA, Director, Division of Technology Development and Transfer, NIH, (2) Raju Kucherlapati, PhD, Scientific Director, Harvard-Partners Center for Genetics and Genomics, and (3) Timothy Stenzel, MD, PhD, Medical Director, Abbott Molecular. Privacy concerns and reimbursement issues were also presented.

### Commercialization Process

Test commercialization is a lengthy process. Laboratory developed tests (LDTs) must be conducted in a laboratory that meets the approval of the Centers for Medicare and Medicaid Services (CMS) Clinical Laboratory Improvements Amendments (CLIA). The product must evolve from an idea to a sellable commodity. For example, a simplified chronological sequence might include:

- Preliminary discovery
- Initial data collection
- A search for IP blocks and the resolution of any patent issues
- Either offer the test in a CLIA approved laboratory, or seek FDA approval for the test.

If FDA approval is sought, then the FDA is brought in for preliminary discussions. If validation and/or clinical trials will be conducted, then it is in the sponsor's best interests to proceed in concert with FDA input.

- Validation or clinical trial
- Preparation of the approval application
- An FDA inspection
- After a thorough FDA review, approval

It is important to remember that patients do not want to wait through a long approval process. Once a discovery is announced, requests for the new test begin. Typically, some of these initial requests are accommodated—provided the test is conducted in a CLIA approved laboratory.

### **Privacy Concerns**

How can privacy be ensured in studies and data collection? Are privacy concerns keeping people from enrolling in genetic testing trials?

One argument is that genetic information is no different than any other medical record. Proponents say that the current Health Insurance Portability and Accountability Act (HIPAA) privacy rule is adequate. Although this is true for the group insurance market, HIPAA does not cover the independent market. Federal employees have additional protection under an executive order, and some states have tighter discrimination standards than the federal requirement. The pending Genetic Information Nondiscrimination Act (GINA) would secure loopholes in HIPAA and alleviate many of these privacy concerns [note 7].

Kucherlapati described the situation at Harvard, in which only the ordering physician has access to a patient's medical record. Because of this, privacy concerns have not affected enrollment in Harvard's programs.

### **Reimbursement**

Many people see reimbursement difficulties as a greater hurdle to commercialization than FDA approval. A reimbursement request must be submitted with a Current Procedural Terminology (CPT) code. By definition, CPT codes only cover current procedures. This creates an obvious mismatch of information when a new diagnostic test is presented to a reimbursement entity. If a genetic test can only confirm a condition for which there is no medical treatment available (for example, Alzheimer's disease), then the test generally does not qualify for reimbursement. This payment structure can discourage individuals from taking the test.

### **Cost and Value**

Are genetic and genomic tests expensive? Some may be expensive in comparison to other diagnostic tests, but the value they impart must also be considered. Cost and medical benefit must be considered jointly, along with other factors. Genetic information provides psychosocial, familial, educational, and economic benefits for individuals and families, as well.

## **What Needs Oversight and Who Should Do the Overseeing?**

This question was debated over a lively dinner. Stuart Hogarth, PhD candidate, Research Associate, Cambridge University, moderated. The debaters were (1) David Mongillo, MPH, Vice President for Policy and Regulatory Affairs, American Clinical Laboratory Association (ACLA), and



(2) Janet Woodcock, MD, Deputy Commissioner, Chief Medical Officer, FDA. There were two key questions posed at the debate:

- What aspects of genetic testing need oversight?
- Who should have oversight authority?

### **FDA Perspective**

Woodcock provided the FDA's perspective. She noted that while there is no perfect path, the FDA tries to encourage innovation while protecting the public from fraud. A strong regulatory framework is actually conducive to competition.

Genomic testing and pharmacogenomics are different than classic genetic testing. Classic genetic testing is readily interpretable by clinicians, but this new generation of test results does not clearly tell the recipient what to do. Therefore, without proper regulation, the public faces several risks from the use of complex tests:

- Economic health fraud is a reality.
- DTC tests pose special risks when there are no specialists (healthcare providers or genetic counselors) involved in the process.
- More complex tests are being developed that include multiplex testing and algorithms to determine the result.
- A lack of regulation discourages reimbursement. A test developer then carries the risk that it may not receive payment for a test.

### **ACLA Perspective**

Mongillo represented the perspective of ACLA, a non-profit membership organization of clinical laboratories. Mongillo said that DTC tests—especially those conducted without the benefit of a physician and a genetic counselor—and tests that fall outside of CLIA specifications need regulation.

According to Mongillo, CLIA provides adequate oversight and lab tests are already highly regulated. He pointed out that the FDA could have a valid role in genetic testing oversight, but that the expertise that is already available through CLIA is sufficient, and an added layer of regulation would be redundant. He suggested that genetic tests may not warrant special consideration, and perhaps there is too much emphasis on unwarranted “genetic exceptionalism.”

Regulation should move forward in those areas that have the highest risk. Established tests do not need additional regulations.

### **Audience Input**

The audience was asked to comment after the debaters stated their positions. In general, several consensus points were reached:

- Appropriate regulation is necessary and good.
- It is important that flexibility be built into the regulatory scheme.
- DTC testing needs special attention.
- Regulation should be risk-based. One set of standards will not fit all tests.
- Claims and results interpretations should be subject to regulation.
- Good regulations have clarity, stability, transparency, and proceed with incremental change.

The following recommendations were made:

- The newborn screening panel of tests should be federally mandated to create parity. Currently, there is a wide variation from state to state.
- Professional associations should participate in offering models for oversight schema.

- Genetic counseling should be mandatory for testing that leads to life-changing decisions.
- A registry should be established with the goal of eventually making this registry mandatory.

On the specific topic of who should provide oversight, various opinions were heard, but no consensus was reached:

- The Federal Trade Commission (FTC) should do more to ensure truth-in-advertising.
- The combination of FTC, CMS (through CLIA), and FDA structure is sufficient but there should be better enforcement of existing regulations.
- Professional organizations should increase their level of participation in voluntary monitoring mechanisms and in dialogue with federal agencies.
- Test interpretation should be regulated because the interpretation is the final product.
- Test interpretation should not be regulated because it is clinical practice.
- Focus should be on just the bad actors.

### Notes for Day One

1. *Personalized Healthcare: Opportunities, Pathways, Resources*. United States Department of Health and Human Services (HHS) (September 2007), p. 65. See also <http://www.hhs.gov/myhealthcare/>.
2. *Personalized Healthcare*, HHS, p. 11.
3. McLeod referenced a statement by Collins from TIME magazine's "The Future of Life" symposium (2003). See <http://thefutureoflife.com>.
4. See <http://www.fda.gov/bbs/topics/NEWS/2007/NEW01684.html> for the August 16, 2007 FDA release.
5. *The Cancer Genome Atlas*. National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI), <http://cancergenome.nih.gov/>.
6. See <http://www.genome.gov/24519851> for the NHGRI description of GINA.
7. See <http://www.genome.gov/10002328> for NHGRI's "Genetic Discrimination in Health Insurance" fact sheet.

## Ensuring Laboratory Quality

The second day of the Summit opened with a panel that brought together representatives from three sectors; government agencies, professional societies, and policy organizations discussed quality control in the laboratories that perform genetic tests.

Kathy Hudson, PhD, Director, Johns Hopkins Genetics and Public Policy Center (GPPC), served as the interviewer. The other panelists were (1) D. Joe Boone, PhD, Associate Director for Science, National Center for Preparedness, Detection, and Control of Infectious Diseases, Centers for Disease Control and Prevention (CDC), (2) Gail Vance, MD, FCAP, Professor, Department of Medical and Molecular Genetics, Indiana University, College of American Pathologists (CAP), and (3) Judy Yost, MA, MT, Director, Division of Laboratory Services, Centers for Medicare and Medicaid Services (CMS).

### Current Regulation Structure

Hudson opened the conversation with a question: What grade would you give current lab quality?

Vance said she would give it an “A.” CLIA is very important, and professional organizations can extend and improve upon CLIA’s standards. Boone declined to offer a grade, but commented that genetic testing labs engage in more self-policing than labs that perform other types of tests. All types of testing have some problems, and Boone would like to see professional organizations take on a bigger oversight role.

Yost insisted that CMS is committed to continually evaluating its oversight mechanism and stressed the importance of continuing education for all participants: lab personnel, CMS surveyors, and the public. CMS educational initiatives include periodic training for the people who assess lab compliance. Yost also noted CDC initiatives, which include the Morbidity and Mortality Weekly Report (MMWR).

Hudson called CLIA a “regulatory floor” for laboratory standards, and noted that beyond the baseline set by CLIA, standards vary by state. New York, for example, has the most rigorous regulations.

The College of American Pathologists (CAP) is one of six laboratory accrediting organizations. In addition to legally mandated quality control requirements, CAP has a voluntary laboratory accreditation program. Vance described the program requirements:

- internal lab quality control
- external inspection once every two years
- proficiency testing

CAP inspections can have punitive results. Laboratories are required to submit corrective plans of action if deficiencies are found.

### Proficiency Testing

Vance commented that all high complexity labs – not just those labs performing genetic tests – should do proficiency testing (PT). The proficiency test essentially serves as a quiz. The lab is given an unknown specimen to test, and its results are evaluated.

Yost and Hudson discussed CMS’ 2000 issuance of a Notice of Proposed Rulemaking for a CLIA genetics specialty, which they reiterated in 2006, and then decided to abandon. Hudson described the petition Genetics and Public Policy Center, Genetic Alliance, and Public Citizen sent to CMS to ask them to proceed with the establishment of a genetics specialty. Yost confirmed CMS’s response that rulemaking is too burdensome and not needed.

Later in the discussion, an audience member presented the perspective of a small, high-complexity testing lab. Such a facility performs highly complex tests and recognizes the need for an increased level of PT. However, the cost of increased PT can be prohibitive, and platform-based PT was presented as an alternative. Both Boone and Vance acknowledged that platform-based PT could be a viable alternative.

Boone noted that there are approximately 200,000 labs in the U.S. Eighty percent of those labs are not performing high complexity testing; the remaining 20% are moderate or high complexity labs.

### **Clinical Validity**

Hudson stated that ensuring analytical validity is CLIA's role. She then asked the panelists if clinical validity also falls under CLIA's purview.

Yost agreed that analytical validity is the basis of the CLIA laws. She said that CMS should not determine clinical validity, as other organizations already have the necessary expertise to perform that function. Vance commented that the CLIA regulations do contain indirect references to clinical validity, and reminded the panel that laboratories are under great pressure to release tests, even without demonstrated clinical validity.

All panelists expressed strong support for letting public-private partnerships determine clinical validity. There was some concern about the difficulty of ensuring success when public and private entities have such different perspectives and work methods. But overall, stakeholders were enthusiastic about third party review through a public-private enterprise.

## **Discussion of the Role of FDA in Oversight**

This discussion brought together individuals who work closely with FDA regulations. The focus of the conversation was the FDA's legal authority and proper implementation of its oversight function. Jonathan Rockoff, Reporter, Baltimore Sun, served as interviewer. Other panelists included (1) Jeff Gibbs, JD, Director, Hyman, Phelps & McNamara, P.C., (2) James Kelly, PhD, Senior Director, Regulatory Affairs, Roche Diagnostics, (3) Paul Radensky, MD, JD, Partner, McDermott Will & Emery, (4) Bradley Thompson, MBA, Esq., Epstein Becker & Green P.C., and (5) Daniel Troy, JD, Partner, Sidley Austin Brown & Wood LLP.

### **FDA Authority**

Rockoff's opening question provoked conflict: Does the FDA have the authority to regulate genetic tests? The question received the following responses:

- The FDA has the authority to regulate test kits but not LDTs.
- It remains questionable whether or not LDTs meet the FDA device definition.
- The FDA definitely has the authority to regulate LDTs. There is no doubt that these tests are products.

At present, the FDA regulates test kits—products that are manufactured for use in a laboratory to perform a laboratory test. It has not regulated LDTs—tests that are created and conducted in-house—although it may regulate the components of the test. Thompson pointed out that the FDA has not hesitated to exert its authority before, and he cited pharmacy compounding as an example. Pharmacists were given latitude to create compounds, but were still subject to regulation. Once pharmacists began pre-making batches of compounded drugs, however, the FDA decided that they were no longer simply providing a service, but in fact had become product manufacturers. Another example is single-use devices. The FDA decided to hold hospitals accountable for reprocessing these devices.

Gibbs noted that the legal accuracy of the FDA's position—that compounded drugs are new drugs—is debatable. Applying the analogy of compounded drugs to LDTs makes all LDTs illegal.

### Current Regulatory Scheme

According to Troy, the FDA is trying to draw the line between the bad actors and the good actors. To this end, the FDA is attempting to intervene in problematic tests while avoiding unintended consequences, such as declaring all LDTs illegal, an effort termed enforcement discretion. The panelists listed several problems with the current state of FDA oversight:

- Enforcement discretion is problematic since it creates an unpredictable climate.
- Regulation is currently “who-based” instead of risk-based.
- There are places within the regulations where the FDA and CLIA overlap or even conflict.
- The “shall not be used for treatment” label may lead to a lack of reimbursement.

Troy noted that the FDA needs to engage in rulemaking. This action would be in the FDA’s best interest because it would provide the agency with Chevron deference, a favorable legal position [note 1].

### FDA Guidance

Rockoff asked: How can we best fashion FDA oversight?

Gibbs remarked that guidance documents are supposed to provide clarification about regulations. For example, the FDA has released a final ASR guidance document and a draft In Vitro Diagnostic Multivariate Index Assay (IVDMIA) guidance document [note 2]. However, some of the panelists thought these releases go beyond clarification and present new rules. Gibbs noted that it is difficult for labs to know what these FDA guidance documents mean for day-to-day operations because they do not include practical details. Kelly agreed that clear guidance would benefit industry by helping companies plan resources and timelines in advance.

Thompson presented two methods for resolving current policy issues. The first, a long-term solution, entails FDA rulemaking to determine a scheme to stratify tests by risk. A more expedient solution would be to apply the nine factors that guide pharmacy compounding to genetic tests.

### Suggestions for Improvement

The panelists, with participation from the audience, suggested several improvements to FDA oversight of genetic tests:

- The genetic testing field contains rapidly changing technology, but other aspects of medicine can provide insight.
- The FDA needs more resources—especially expertise.
- It is incumbent upon companies not to surprise the FDA. The process does not flow well when the company knows more than the FDA about a submittal. The FDA is then inclined to withhold its imprimatur.
- Companies have to put time and resources into developing good studies.
- Companies need clear benchmarks for what constitutes evidence.
- Manufacturers have the responsibility to develop safe and effective tests.
- The FDA should provide consistent and meaningful feedback to manufacturers, but not change its position after initial feedback is given.
- A mandatory registry would help, but there are costs associated with collecting the data. The benefit/burden would need to be analyzed. One method might be to expand existing CLIA databases or to collect adverse experience data.
- Data collection to determine if LDTs perform as well as FDA regulated test kits would be of great value.

- FDA regulations need to avoid making it too hard to put a product in the marketplace or too difficult to make product changes.
- Is genetic testing a manufacturing process? Is the end product a device or information? The answers to these two questions are critical.

### A Variety of Perspectives

The audience presented additional comments from a variety of perspectives. A genetic counselor suggested that harm could come from several sources. The problem is not necessarily the lab. Rather, problems such as informed consent, interpretations, and conversations with the patient are rampant in other parts of the process.

An investor noted that requirements for more rigorous testing will require more dollars to flow in from investment capital. Regulators need to realize that changing the rules midstream discourages investment.

From an industry perspective, regulation is inherently constraining, and the FDA has inserted a level of instability in the regulatory scheme. But industry actually likes regulation because it keeps the bad actors out of the marketplace. If the U.S withholds approval, the technology will not disappear, it will go overseas.

It was suggested that responsibility for tests that do not have a high degree of risk could be given to a third party. However, third party review systems present legal hurdles, and the FDA has difficulty delegating its “blessing authority.”

## FDA Response

Janet Woodcock, MD, Deputy Commissioner, Chief Medical Officer, FDA, responded to the discussion about the FDA’s role in genetic testing.

She began by outlining the historical trajectory of the regulations, and then addressed various points of the conversation in turn. In the 1990s, the FDA undertook ASR regulation and thus created a scheme that ensured the proper production of reagents. CLIA was established as a quality system for labs, but currently CLIA is not capable of determining clinical utility.

The industry grew rapidly and LDTs became successful and widespread. Industry continued to advance and develop new technologies, and the definition of ASR was no longer clear. Because of misinterpretations, the FDA issued an ASR guidance. The FDA has also issued an IVDMIA guidance.

The newest types of tests, like pharmacogenomics, determine dosage and treatment. There is more at stake with tests that do more than diagnose. Clinical interpretation is more difficult with IVDMIA; the average clinician is unable to interpret them.

The current scheme of enforcement discretion is not a good paradigm.

The FDA’s current position is that LDTs are considered medical devices, but the FDA has not proposed regulation for most LDTs. Ultimately, the courts will decide this issue.

Woodcock expressed disappointment that investors perceive the FDA as an entity that makes unpredictable changes. She said that open discussions with industry are valuable, and noted that all stakeholders (including government employees) become frustrated with excessive bureaucracy.

The FDA issues guidance documents because regulations take a protracted amount of time. Statutory changes are issued “once in a lifetime.”

Woodcock is not convinced that adverse event recording is valuable. Are the consequences of a given test really known? An outcomes assessment would be needed, but this is a costly solution.

She concluded by asserting that the data obtainable from the new generation of genetic tests is important information and admitted that federal agencies are struggling through the process of replacing old schemes. But she was ultimately optimistic: the future is bright for the public.

## Breakout Groups: Reimbursement, Regulation, Policy and Legislation

A working lunch followed the FDA discussions. Summit participants were invited to choose one of the three breakout groups. After lunch, a representative from each group reported a concise summary of the conversations.

### **Reimbursement**

Reimbursement is part of the genetic testing pipeline, and various stakeholders—professional organizations, advocacy groups, physicians, and laboratory personnel—have roles in the process. Coding methods and fee schedules need to be improved.

### **Regulation**

The goal is to provide patient access to safe tests without placing an undue burden on industry through excessive regulation.

### **Policy and Legislation**

It is important to remember the power of Congress and its ability to be politically responsive. However, legislation is a slow process. Active pieces of legislation with direct relevance to genetic testing include the Genomics and Personalized Medicine Act of 2007, which was introduced in the Senate and has been referred to committee, and the Genetic Information Nondiscrimination Act (GINA) of 2007, which has been passed in the House and is pending vote in the Senate.

## Role of Professional, Laboratory, and Patient Guidelines and Best Practices: the Cystic Fibrosis Guidelines Testing Story

The genetic test for cystic fibrosis (CF) carrier screening is well-established. In 2001, the American College of Obstetricians and Gynecologists (ACOG) released test guidelines for physicians, and the American College of Medical Genetics (ACMG) released guidelines for laboratories. The impact of these guidelines has been followed and evaluated. Newer genetic tests can incorporate the lessons learned and apply them to future guidelines.

The presenters were (1) Deborah Driscoll, MD, Professor and Chair, Department of Obstetrics and Gynecology, University of Pennsylvania Medical Center, (2) Kathy Hudson, PhD, Director, Genetics and Public Policy Center (GPPC), and (3) Jeffrey A. Kant, MD, PhD, Professor, Pathology and Human Genetics and Director, Division of Molecular Diagnostics, University of Pittsburgh Medical Center.

The CFTR gene (the gene associated with cystic fibrosis) and its common mutations were identified in 1989. In 1997, the NIH held a Consensus Development Conference and called for population-based screening for CF. As noted above, clinical and laboratory guidelines for carrier screening were released in 2001. Two years after the guidelines were released, a survey was conducted to evaluate implementation by physicians [note 3], as a result of a number of concerns about issues such as provider's interpretation of test results and the adequacy of both pre-test and post-test counseling.

According to Driscoll, the goals of CF carrier screening are to identify couples at risk for having children with classic CF and to allow couples to make informed reproductive decisions.

The purpose of the guidelines was to:

- educate physicians about CF
- provide a model for implementing CF carrier screening into routine practice
- provide materials to assist with implementation (such as consent forms and patient education brochures)
- provide recommendations for who should be offered CF carrier screening

The survey focused on two questions:

- How familiar are obstetricians and gynecologists with CF carrier screening guidelines?
- Do the guidelines impact their practice behavior?

The survey concluded that doctors were doing a good job with their pregnant patients, but there was substantial room for improvement with the non-pregnant patients. Driscoll explained that patients find it difficult to get reimbursement for preconception carrier screening.

Driscoll discussed the lessons that have been learned through the CF carrier screening program.

In summary:

- Guidelines have a significant impact on practice behavior.
- Guidelines are an important source of information to providers.
- It is important to keep guidelines simple. Doctors want to be told what to do.
- Providers need continuing medical education in order to increase their comfort level with the results and to help them better counsel their patients.
- By educating the public, the public will become more proactive in its requests for testing.
- Alternative venues for reaching providers are needed.

Hudson then addressed laboratory compliance with the guidelines. From December 2005 to March 2006 an array of data was collected by GPPC about CF carrier screening clinical lab practices and the opinions and attitudes of the lab directors.



According to Hudson, the current ACMG guidelines state that:

- Labs should routinely screen for only 23 mutations.
- 5T had been tested only as a reflex to a finding of R117H, since R117H has a complex association with the 5T/7T/9T variants.
- It might be appropriate to test additional alleles, depending upon the race and ethnicity of the population being tested.

The initial guidelines are now six years old. The GPPC survey asked: How are the labs doing?

It was found that only 10% of labs are in compliance with the recommended 23 mutation screening panel. The other 90% test more than 23 mutations. Labs are doing a better job complying with the 5T reflex recommendation, with seventy-five percent performing the test in accordance with the guidelines. However, overall, only 7% of labs are in compliance with both recommendations. Thirteen percent of labs are in compliance with neither guideline.

Why are the compliance rates so low on the mutation screening panel recommendation? Hudson proposed some questions, which, when answered, might explain the statistics:

- Are the guidelines not useful? Are they out of date?
- Are providers and patients demanding that more than 23 mutations be tested?
- Are expanded panels being used to accommodate the racial and ethnic diversity of the population being tested?
- Are the available testing platforms driving the number of mutations that are being screened?

Beginning with the belief that compliance with guidelines improves outcomes—and perhaps more research is needed to confirm that belief—how can better compliance with existing guidelines be encouraged? Hudson offered some ideas for consideration:

- Would linking compliance to reimbursement be useful?
- Should compliance be linked to oversight?
- Would embedded, electronic medical records be helpful?
- Are concerns about liability driving lack of compliance?
- Do better decision making tools need to be developed?

Kant also provided insight into the CF laboratory screening guidelines and current issues surrounding the test. One of the most important items the lab generates is the report. The report is for both the clinician and the patient; in fact, many patients ask for their report. Kant described the type of report that his lab provides, which consists of two sections: interpretation and results.

The interpretive section contains the essence of the information. For a negative result, the report might say “no mutations identified using a recommended screening panel.” For a positive result, the report would name the discovered mutation and recommend testing of the patient’s partner and relatives.

In the results section, the report gives a brief description of the disease. It emphasizes that carrier rates vary by ethnicity and that a negative result retains a residual carrier risk. The lab report provides details about the residual risk.

He explained the logistics of CF testing. Many times the patient has received a prescription for the test and has a blood sample drawn at a local draw station. It is not always possible for the lab to know the reason for the test—is it carrier testing or is the patient symptomatic? The screening panel is not optimal for diagnostic testing, but it is a useful starting point.

The providing physician obtains the formal consent form. Genetic testing is a process, and consent is only one part of the process. Labs take great care to convey information in a report that is both accurate and useful, but it is not uncommon for results to be provided over the phone with little detail. There needs to be adequate post-test review with negative-result patients in order to convey residual carrier risk. Positive-result patients should receive formal genetic counseling. Sometimes, the implications for relatives are not discussed in detail. Kant commented that “what the patients actually take away from the laboratory test” varies greatly.

Physicians and patients want their results as quickly as possible, which places financial pressures on labs. Labs are often presented with questions about reimbursement, but this information is not readily available to them. Labs do supply CPT coding, and the codes often confuse the payers.

## Practice of Medicine

Once a genetic test is complete, the results have to be interpreted by a professional and then delivered to the patient. When you move from performing a test to interpreting a test, you enter the realm of medical practice and clinical utility.

This discussion explored the practice of medicine from the perspectives of primary care physicians and pathologists. It also emphasized the unique needs of rare disease programs.

The panelists were (1) Andy Faucett, MS, CGC, Chair, Collaboration, Education, and Test Translation Program (CETT) and Emory University, (2) W. Gregory Feero, MD, PhD, Chief, Genomic Healthcare Branch, National Human Genome Research Institute, NIH and (3) Margaret Gulley, MD, Molecular Pathologist and Geneticist, University of North Carolina (UNC) Department of Pathology and Laboratory Medicine. Sharon Terry, MA, President and CEO, Genetic Alliance, moderated this panel.

### Rare Diseases

Faucett opened the discussion by describing the CETT program model. CETT “promotes the translation of rare disease genetic tests from research to clinical laboratories. This is achieved through collaborations among clinicians, laboratories, researchers and patient advocates” [note 4].

It can be difficult for rare disease programs to receive adequate attention and funding. It can also be challenging to locate and enroll enough patients to support the necessary studies. During the course of this Summit, a great deal of support was expressed for a risk-based regulations scheme. Faucett cautioned that rare disease testing could suffer under such a scheme. A test could have a high degree of risk but a low demand in the marketplace, a scenario that provides no financial incentive for investors. Conversely, CETT may prove to be a good model for moving tests from research to clinical practice, both in its assessment of what constitutes clinical utility and in its collaborations between researchers, clinicians, laboratories and advocates.

### Primary Care Physicians

The primary care physician (PCP) is often the individual who receives genetic test results from a laboratory and then has the responsibility of transferring the information to the patient. Feero presented the primary care physician's perspective. Primary care physicians assume analytical validity. They question the clinical validity and clinical utility of tests. The key question for the PCP is whether or not the test will benefit the individual patient. Everyone who is involved in genetic testing must realize that PCPs are extraordinarily pressed for time. Most PCPs see a high volume of patients. PCPs need results that are clear and concise, and they need help with interpretation—they do not have time to do the homework.

### Pathologists

Gulley presented the pathologist's perspective on genetic testing. Pathologists are highly trained physicians. After their medical training, they spend four years in the lab. Pathologists interpret test results as a service to physicians.

Every CLIA-certified lab is required to have certain personnel on staff. It must have a:

- doctor of medicine
- lab director
- technical supervisor
- clinical consultant

CLIA regulations detail the education, certifications, and responsibilities of lab personnel. The clinical consultant “must be qualified to consult with and render opinions to the laboratory's clients concerning the diagnosis, treatment and management of patient care” [note 5]. Thus, laboratories ensure “not just a test that's done right but that the right test is done.”

Research laboratories such as Gulley's often need to decide when a test is ready to “go live,” or be offered to the public via a physician. How much evidence is adequate? Molecular pathologists often cannot wait for perfect evidence. This decision can be especially difficult to make in the case of rare disease tests.

Gulley described her judgment process, during which she asks herself two questions:

- Would I give this test to my loved ones?
- Can I imagine myself in a courtroom adequately defending my decision to go live with the test?

### Tension Between Science and Art

Terry commented that there is tension between the art and science of medicine, and she asked the panelists how that tension influences their worldview. Feero replied that the clinician needs wide latitude to make decisions, but once a test becomes commonplace a decision-making protocol is usually established. Gulley said that she believes in evidence-based medicine but realizes that there are not enough resources available to thoroughly investigate every test.

Tests do reach the marketplace with knowledge gaps still in place. Is post-market test data good for filling in those knowledge gaps? It is difficult to find funding for data collection and analysis once a test is on the market. The CETT program provides a fantastic model for data collection, but it has very limited funding. Manufacturers would be the best source of funding for this data, but they have biases.

Panelists commented on educational information:

- There is a wide variance in the quality of information patients receive.
- Lab reports should be limited to one page. Sometimes they are long and complicated because of liability concerns, but the effect is that the core information is not emphasized enough.

## Recurring Themes

By the conclusion of the Summit, a number of recurring themes were evident. The genetic testing landscape is evolving, and difficult questions remain unanswered.

**Biobanks.** How important are they? Who should maintain them?

**Costs and Value.** The costs associated with older tests may drop. But the newer, more complex tests are constantly being developed, and they are expensive. How do we determine the value of a test? Do we only look at its economic benefit or do we also look at ethical, legal, and social factors?

**Direct-to-Consumer Tests.** It is important to distinguish between marketing tests directly to consumers and selling tests directly to consumers. It is also important to distinguish the possible harms from both types of tests. How can the public be protected from fraudulent or exaggerated claims, and/or invalid or useless tests?

**Education.** It is of paramount importance that better education materials and vehicles be developed and promoted. The entire spectrum of the population needs more and better education about genetic testing. Patients, Congress, physicians, laboratory personnel, and regulators are just some of the groups that would benefit from improved education. Education takes many forms, including formal guidelines for physicians, multimedia presentations for patients, and continuing education for healthcare professionals and laboratory inspectors.

**Evidence.** How much clinical evidence is enough? Are the pressures to bring tests into the marketplace overriding the scientific need for evidence? Or are demands for evidence unnecessarily slowing down the approval process? All tests cannot be held to a single standard—there are legitimate variables in the need for clinical data. What role does post-market data play in collecting evidence?

**Genetic Discrimination.** Is genetic data really so different from other medical records? Does it deserve special legislation and protection? Are fears of genetic discrimination keeping people from taking the tests? Summit participants expressed strong support for the passage of GINA.

**Industry Models.** Other industries have wrangled with some of the issues that are currently facing the genomics industry. For example, in the computer industry complex networks and databases are the norm. The music industry has been forced to reexamine its stance on intellectual property. What lessons have been learned in other industries that can be applied to the genomics industry?

**Intellectual Property.** There is a place for patents within the genetic testing industry. Patents provide financial reward, which is inviting to investors. But proprietary information is restricted information. Which types of discoveries should be placed in the public domain? How can you craft an intellectual property policy so that it encourages investment while ensuring adequate access to data?

**Laboratory Developed Tests.** Are they medical devices? Should they be regulated differently than standard test kits?

**Medical Records.** Are electronic, portable medical records important? Would the public support large databases, or would privacy concerns override perceived benefits?

**Personalized Healthcare.** The concept of personalized healthcare is not new, and it is currently practiced. However, the community is striving toward a higher ideal of personalized therapies and interventions based on genetic data.

**Professional Organizations.** What role should they play in regulatory oversight? Are they doing enough? Given that participation in professional organizations is voluntary, how much impact can they have on bad actors?

**Proficiency Testing.** What is the role of proficiency testing in achieving superior quality control? How can you increase the amount of proficiency testing without placing an undue financial burden on small laboratories?

**Public-Private Partnerships.** Summit participants expressed strong support for public-private partnerships. These types of arrangements could go a long way toward relieving the pressures on the current system, but there are legal and cultural aspects to be overcome.

**Rare Diseases.** Rare disease programs often struggle to receive sufficient funding and attention. It can be difficult to collect enough data to conduct a good study. But rare disease programs deserve support. The CETT model has been successful. Can it be expanded to more common tests? Are there particular aspects of the process that need to be reminded of the unique challenges that accompany work on rare diseases?

**Registries.** Should there be data registries for genetic tests? Should they be voluntary or mandatory? What type of data should be deposited? Who should maintain the registries?

**Regulatory Authority.** Who has the regulatory authority for genetic testing? What should be the role of the FDA, CMS, and the FTC? How can the regulatory scheme be sculpted so that it promotes transparency, predictability, and clarity?

**Reimbursement.** Reimbursement has been called the “ultimate bar.” Without adequate reimbursement, it is challenging to achieve wide adoption of an expensive test. But do the payers really understand the value of genetic testing? Is this even the right structure for the healthcare system?

**Resource Allocation.** Funding for research is limited. Patients and reimbursement entities have budgets to maintain. How can we guarantee that everyone has equal access to testing and treatments? How can we ensure that rare disease research receives adequate attention and support?

**Risk-Based Regulation.** This type of regulatory scheme acknowledges the fact that some tests pose more risk to patients and society than others. It is a generally desirable scenario, with allowances made for volume (for example, the low volume of tests for rare diseases).

**Role of Patients and the Advocacy Community.** Patients want to play an ever-increasing role in the treatment decision-making process. But are the physicians really listening to the patients? Advocacy groups are often considered the bridge between the scientific community and the public. It is crucial that they take great care with the messages that they bring to the public.

**Study Design.** Well-designed studies streamline the process of moving a test from the research phase to standard clinical practice. Poor studies undermine the credibility of the industry. What lessons have been learned from previous studies? How can they be applied to future studies?

**Tension Between the Product and the Process.** Technology takes great leaps but behavior has a slow, iterative rate of change.

**Test Interpretation.** Who is responsible for interpreting tests? Who should be responsible for determining clinical utility?

**World Health.** What are the most pressing medical needs of the developing world? How can the transfer of genomics technology to the developing world be streamlined?

## Wrap Up and Next Steps

Sharon Terry, President and CEO of Genetic Alliance, spoke briefly a number of times during the Summit. She provided summaries of the discussions, enumerated the consensus points, and outlined the action steps that need to be taken. She noted the following consensus points:

- There is tremendous goodwill within the genetic testing community – the participants genuinely have their eyes on the prize: health.
- We need to close the knowledge gaps between basic science and the public.
- We need transparency. This can be obtained through “sunshine on the data” and through registries.
- We need clarity and predictability.
- A risk-based regulation scheme is desirable, with the caveat that allowances should be made for volume.
- We need discourse with and responsiveness from the federal agencies that have jurisdiction over genetic testing.
- The FDA needs more people and more money.
- DTC tests need special oversight.
- The industry must have the means to rid itself of bad actors, without crafting oversight based on bad actors.
- Public-private partnerships are desirable.
- Education (at all points in the process) is desirable.
- We need outcomes-data collections and clear evidence bars.
- The NIH needs to put more requirements on its funding so that researchers are developing quality evidence that could become the basis for clinical tests and therapies.

Terry, with input from audience participants, outlined the action steps that are required to move the industry forward:

- Demand transparency.
- Tell the truth.
- Continue to move beyond our turf.
- Create a forum for discourse between CMS and FDA.
- Hold a meeting on reimbursement issues.
- Hold a summit on evidence and outcomes data.
- Hold a summit on third party review systems.
- Explore risk.
- Educate Congress, patients, and clinicians.

- Pass GINA.
- Recognize that this has been a U.S.-centric discussion and that we need to further examine the global perspective.
- Meet with the Secretary of HHS and leadership in all of the agencies to broaden communication and advance solutions.

## Notes for Day Two

1. See *Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc.*, 467 U.S. 837 (1984).
2. *Guidance for Industry and FDA Staff Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions*. FDA (September 14, 2007). See <http://www.fda.gov/cdrh/oivd/guidance/1590.pdf>. *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff In Vitro Diagnostic Multivariate Index Assays*. FDA (July 26, 2007). See <http://www.fda.gov/cdrh/oivd/guidance/1610.pdf>.
3. Morgan, Marie A., Driscoll, Deborah A., Zinberg, Stanley, Schulkin, Jay, and Mennuti, Michael. *Impact of Self-Reported Familiarity With Guidelines for Cystic Fibrosis Carrier Screening*. American College of Obstetricians and Gynecologists (June 2005).
4. See <http://www.cettprogram.org/>.
5. Clinical Laboratory Improvement Amendments (CLIA) Regulations, 493.1417, *Standard; Clinical consultant qualifications*.

## Conclusion

It is clear that this is an area ripe with possibility. It is also clear that lack of leadership and communication in and among federal agencies and other stakeholders, a lag in the time regulation takes to catch up to innovation, and competition across all stakeholder groups has left much fruit on the vine, but with the potential for demise rather than success.

We opened this space to invite truth and honest interactions. We achieved that goal, the result of which is the prior list of recommendations. Following this meeting, a number of companies, academic groups, and advocacy organizations came together to work out concrete recommendations for alternative models. Federal agencies invited input from these and other groups. The community has taken action on each recommendation, some more than others.

The most difficult aspect of releasing the great potential of genetics and genomics as it moves into medicine is not the science, nor the intellectual endeavors. The most difficult task is encouraging honest interactions that will result in the best solutions. Society needs appropriate regulation—benchmarks of the truth that make sense and make products safe. Innovators and entrepreneurs need the same truth—what makes sense and what is safe to pursue. Healthcare providers need assurances that their services will be reimbursed fairly, and they need quality information and guidelines in a timely manner. Timely in this age means quickly, along the lines of the responsiveness of other industries in the information age. Finally, consumers need safe and effective tests, as well as an understanding that they have to be involved in the process from clinical trials to policy-making, both formally and informally.

We are truly excited about the power of diagnostics, from simply knowing the name of a disease (ask any family who has traveled the ‘diagnostic odyssey’) to understanding risk, determining prognosis, managing treatment and planning life events. We eagerly anticipate the solutions that will emerge from keeping our eyes on the prize, and we knowingly step up to the task of working with the broader community for safe, effective testing, and the integration of more genetics and genomics into medicine.

Update: On May 21<sup>st</sup>, 2008, the Genetic Information Nondiscrimination Act (GINA) was signed into law by the President after near-unanimous votes in the U.S Senate and the U.S. House of Representatives.

GINA is federal legislation that provides protections against genetic discrimination in health insurance and employment settings. Current laws do not adequately protect individuals from genetic discrimination. Due to this lack, individuals have been fearful of the misuse of their genetic information. This fear has prevented people from accessing their genetic information. Individuals’ lack of testing denies them important medical information that they could otherwise use to proactively manage their health. The fear of discrimination has also caused a large number of people to opt out of clinical trials, which leads to slower development of treatments and beneficial drugs.

GINA provides legal protections for every individual in the nation. With these protections in place, individuals can feel free to avail themselves of genetic testing and use that information to make more robust medical decisions. Researchers can also select from larger pools of clinical trial participants, thus expediting the research and development process for new therapies. The health insurance protections offered by GINA roll out 12 months after the bill is signed. The employment protections can be fully realized 18 months after the bill signing.



## Glossary

**Allele:** defined by NHGRI as “one of the variant forms of a gene at a particular locus, or location, on a chromosome.”

**Analytic validity:** the ability of a genetic test to accurately and reliably measure the genotype of interest.

**Analyte specific reagent (ASR):** in simple terms it is the active ingredient of an in-house test. The FDA defines it as “antibodies, both polyclonal and monoclonal, specific receptor proteins, ligands, nucleic acid sequences, and similar reagents that, through specific binding or chemical reaction with substances in a specimen, are intended to use in a diagnostic application for identification and quantification of an individual chemical substance or ligand in biological specimens.”

**Biobank:** a project that collects and stores biological samples (and sometimes associated health data), often for the purpose of furthering research.

**Clinical Laboratory Improvement Amendments (CLIA):** legislation passed by Congress in 1988 to establish quality standards for all laboratory testing to ensure the accuracy, reliability, and timeliness of patient test results regardless of where the test was performed.

**Clinical utility:** the value of a test in diagnosing / ruling out a disease, in suggesting treatment or prevention strategies, and in evaluating risks and benefits associated with the test.

**Clinical validity:** the ability of a test to distinguish affected and unaffected populations, including a determination of the probability of being affected.

**Device:** an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary purposes.

**Diagnostic:** a process of identifying a medical condition or disease by its signs, symptoms, and the results of various procedures.

**Direct-to-Consumer (DTC) genetic tests:** in common usage, genetic tests that are marketed and/or sold directly to consumers via television, print advertisements, or the Internet which allow a person access to their genetic information without necessarily involving a doctor or insurance company. It may be more accurate to use terms such as ‘direct-to-consumer marketing’, and ‘direct-to-consumer access.’

**In Vitro Diagnostic Multivariate Index Assays (IVDMIA):** a category of diagnostic tests which includes genetic tests derived from in vitro assays and an algorithm for the purpose of obtaining clinical information that may lead to diagnoses and treatment.

**Laboratory developed tests (LDTs):** tests that are created and conducted within a laboratory for its own use.

**Pharmacogenomics:** defined by HHS as the “study of how variations in the human genome affect an individual’s response to medications.”

**Pharmacy compounding:** described by the FDA as a “practice in which pharmacists combine, mix, or alter ingredients to create unique medications that meet specific needs of individual patients.”

**Proficiency testing:** Proficiency testing schemes operate by providing participating laboratories with samples containing specified material but the actual substance is known only to the organizers. The laboratory analyzes the samples, preferably as part of its normal routine, and reports the results to the scheme organizers. The laboratory is then provided with a report showing how closely its results agree with the accepted value. If necessary, the lab can then take appropriate action to improve performance.





4301 Connecticut Ave., NW, Suite 404  
Washington, DC 20008  
T: 202.966.5557 F: 202.966.8553

[WWW.GENETICALLIANCE.ORG](http://WWW.GENETICALLIANCE.ORG)



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