BRINGING GREAT SCIENCE *to Patients*

6th Annual Diagnostics Summit

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California Healthcare Institute

Molecular Diagnostics: Promise and Perils

Molecular diagnostics have the potential to change the practice of medicine. Emerging technologies that rapidly discern an individual's risk to develop a life-threatening disease, or the underlying mutations that drive a patient's cancer, can inform a series of critical healthcare decisions.

"Next generation sequencing has the possibility, on the horizon, to make cancer a chronic disease," said Ronnie Andrews, whose company Thermo Fisher Scientific hosted the event.

However, there are still many hurdles to overcome before this promise can be fully realized. On the regulatory side, the U.S. Food and Drug Administration (FDA) recently decided to regulate laboratory-developed tests (LDTs). Prior to this decision, these diagnostics had been subject to CLIA oversight. However, this changing regulatory landscape poses more questions than it answers as the FDA plays catch-up, trying to understand complex tests with few, if any antecedents to guide them.

Reimbursement is also an issue. Many molecular tests are expensive to develop and produce; however, both public and private payers have been reluctant to fully compensate diagnostics companies for their products without extensive proof of value.

At this point, even the science is far from settled. What constitutes an actionable result? Generally, mutations cannot be measured as binaries: dangerous/not dangerous. Rather, their risks can only be quantified by percentage. If a woman's genetics indicate she has close to a 100 percent chance of developing ovarian cancer, this information provides strong support for her to decide to have her ovaries removed. But what if her risk is 30 percent? 10 percent?

Over the course of CHI's Diagnostics Summit, experts from around the country addressed these and other difficult issues, trying to delineate the best path forward for advanced diagnostics. Ultimately, this discussion will inform policymakers, supporting their efforts to advance California's life sciences ecosystem.

SUMMIT AGENDA

Opening Remarks
Ronnie Andrews, President of Medical Sciences, Thermo Fisher Scientific

Regulatory Approaches to Diagnostics Innovation
Eric Zimmerman, Partner, McDermott Will & Emery

Lakshman Ramamurthy, PhD, Director of FDA Strategy and Regulatory Policy, Avalere

21st Century Cures Initiative
Eric Zimmerman, Partner, McDermott Will & Emery

Driving Toward Value: Ensuring Access to Innovation in New Payment Models
Bruce Quinn, MD, PhD, Senior Health Policy Advisor, Foley Hoag LLP

*Danielle Scelfo, Senior Director of Government Affairs & Public Policy, Genomic Health**

Public Investment in Early-Stage Diagnostics Research
Wendy Rubinstein MD, PhD, Director, NIH Genetic Testing Registry

Gene Sequencing: Early Signals for Clinical Relevance
James Ford, MD, Director, Stanford University Clinical Cancer Genetics Program

Phil Febbo, MD, Chief Medical Officer, Genomic Health

Patient Perspective
Laurie Levin, Cancer Survivor and Advocate

"Next generation sequencing has the possibility, on the horizon, to make cancer a chronic disease."

—Ronnie Andrews, Thermo Fisher Scientific

Regulation and Reimbursement

Developing a groundbreaking genomic test is only the beginning. Companies must also demonstrate the test's effectiveness to the FDA and its value to public and private payers.

On the FDA side, their recent decision to regulate LDTs for safety and efficacy has generated confusion. In the long run, FDA intervention could clarify these rules. However, this will be a protracted process, during which companies may be unclear what they need to show the FDA to gain approval.

"With next gen sequencing, the FDA is figuring it out: How do we use existing constructs to approve these novel products?" said Dr. Lakshman Ramamurthy during the *Regulatory Approaches to Diagnostics Innovation* discussion.

There's a great deal of debate over how the FDA should approach these tests. For example, should they use existing systems or create new regulatory frameworks from scratch?

"If we start over, I'm not sure how we'd craft the appropriate structure, given that we're not really sure how all this is going to end up," said Ronnie Andrews.

The bottom line is the FDA needs help, and the life sciences industry is the only place they can find that support.

"Right now is a good opportunity to engage with them in a positive, non-condescending way," proposed Dr. Ramamurthy.

Communicating with Payers

Reimbursement is equally complicated. Many of these tests are quite expensive. However, by identifying the patients who most benefit from a costly therapy, they can ultimately save money and prove their value.

During the *Driving Toward Value* segment, Dr. Bruce Quinn noted that diagnostics face a number of headwinds. For example, in some circumstances, Medicare is bundling lab tests with doctor visits. "They're like napkins or forks at McDonalds, they're just bundled," Dr. Quinn noted. "Also, if you're a new lab, the day you open up you're out of network with every payer in the United States. That means you have little leverage in asking them to pay you."

Dr. Bruce Quinn, Foley Hoag

Dr. Quinn also delved into how complex it can be to simply figure out who the payers are. Pricing reforms under the Protecting Access to Medicare Act (PAMA), delivery system reforms, including accountable care organizations (ACOs) and other recent changes have created a fragmented landscape. To succeed, diagnostic companies must treat payers as customers. We need to work toward a better way for Companies and payers must find the best ways to assess the value in diagnostic tests. Quinn points to Dr. Felix Frueh's six questions as guidelines *(see sidebar).*

Dr. Quinn and others noted that these complicated decisions will require extensive cooperation between industry, regulators, payers and policymakers.

DIAGNOSTIC FACTS

1%	of marketed drugs have a companion diagnostic
10%	of marketed drugs recommend genetic testing for optimal treatment
33	pharmacogenomic biomarkers are included on FDA-approved drub labels
30%	of all treatments in late clinical development rely on biomarker data
50%	of all treatments in early clinical development rely on biomarker data
60%	of all treatments in preclinical development rely on biomarker data
50%	of all clinical trials collect DNA from patients to aid in biomarker development

Source: Personalized Medicine Coalition

Six Questions to Determine Value

In 2013, Felix Frueh, PhD, chief scientific officer at Human Longevity, Inc., developed six questions to help illuminate a diagnostic test's overall value. Throughout the Diagnostics Summit, speakers referenced these questions to provide a framework for the discussion.

1. **Who are the patients and what are the indications?**
2. **Why is this test better than what we have?**
3. **How is the patient better off?**
4. **Is there something we can do with it?**
5. **Can we use it?**
6. **Will we use it?**

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LIFE, CHANGING.

Policy Solutions

The government is not blind to the potential of next generation diagnostics and is making efforts to support the industry. One of these is the 21st Century Cures Initiative.

Spearheaded by members of the House Energy and Commerce Committee, the proposed initiative would help accelerate the development of new treatments and diagnostics. The concern among policymakers is that great science is being conducted in labs, but these breakthroughs are not making it to patients. To reform how the nation develops drugs, the committee is reviewing the entire cycle of innovation: discovery, development and delivery. In particular, they are focusing on clinical trials, investment,

Genomic Health's Path to Success

Genomic Health provides a case study in how to navigate the regulatory and reimbursement issues that face all diagnostics companies. Speaking immediately after Dr. Quinn, Danielle Scelfo* spoke passionately about the need for more and better data. Companies must show, definitively, how a test will help patients.

"A test can tell you if you have a certain gene or not, but if you can't actually apply that to a change in treatment decision, payers view it as a nice to know but not a need to know," said Scelfo. "We needed to articulate an easy to understand description of the test and downstream implications to provider/patient treatment decisions in order to achieve support and ultimate coverage from the payor community."

Genomic Health's Oncotype DX diagnostic succeeded because it answers key questions. What treatment decisions would be made based on the results of these tests? Does the patient need surgery, chemotherapy or radiation? Do they have aggressive disease? These issues drive payer decisions. By proving their tests personalize treatment and prevent overtreatment, Genomic Health demonstrated the value of their technology.

Scelfo noted that having this value story paved the way for coverage and reimbursement. Genomic Health conducted 14 studies with 14,000 patients. In other words, they produced loads of evidence to show payers.

Danielle Scelfo, Genomic Health

However, it's important to stay consistently on message—for everyone. Sometimes an industry can be its own worst enemy.

"The message that the cost of sequencing is plummeting, can be antithetical to coverage and reimbursement when there is a high bar of evidence required for test adoption," said Scelfo. "We must stress value. Costs have come down, but they certainly aren't free or even a $100."

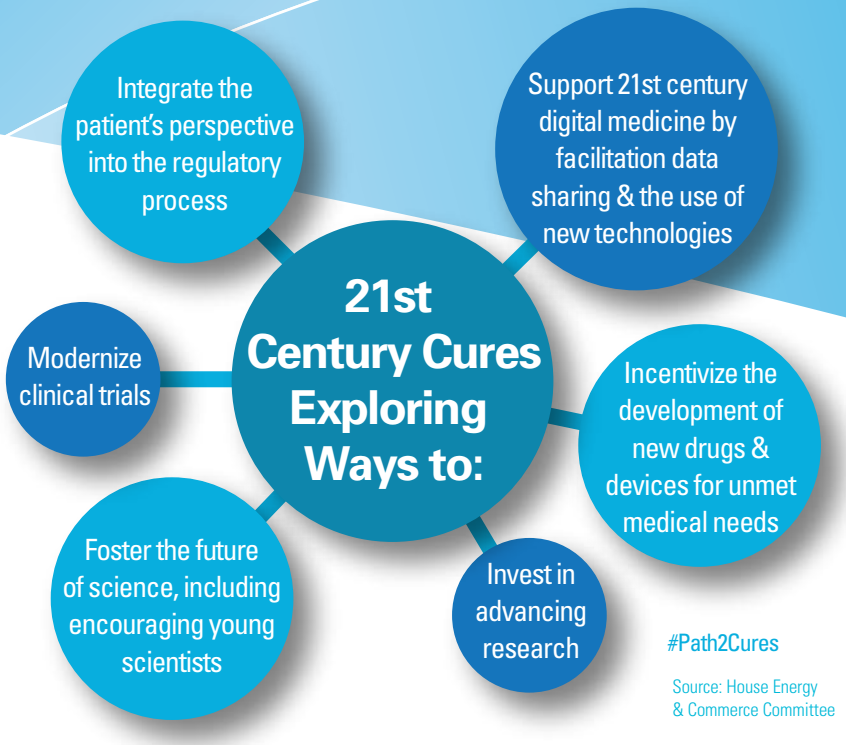
"We need an easy to understand description of the test and downstream implications to the patient."

—Danielle Scelfo, Genomic Health*

*Danielle Scelfo is now Vice-President, Government Affairs and Reimbursement for Adaptive Biotechnologies

personalized medicine, digital health and laboratory developed tests. The committee has held numerous hearings to get a better handle on the problem. But at this point, it's unclear how this will play out.

"It may be that FDA is given free rein to finalize the (LDT) guidance," said Eric Zimmerman. "Or it could be that Congress steps in and completely redirects the FDA."



NIH Genetic Testing Registry

There are many basic questions that need to be answered about molecular diagnostics, such as how many there are and what do they do? To gather this information, the National Institutes of Health has created the Genetic Testing Registry (GTR). Companies voluntarily submit information about their tests to the GTR, creating one central database to clarify which tests are available and how they help patients.

"We're in the information gathering stage," said Dr. Wendy Rubinstein, who directs the registry. "What is their basis? Analytical validity, which CLIA covers; clinical validity, which the FDA covers; clinical utility, which is where the rubber meets the road."

By encouraging labs to report this data, the NIH hopes to increase our understanding of genetic tests and help providers find the right ones for patients.

As of September 2014, the database and public website included more than 20,000 tests for 4,600 conditions and covered 3,200 genes. In addition to recording which tests are out there, a companion resource called ClinVar encourages data sharing on which genetic variations contribute to disease.

"The value is linking the data to actionable outcomes," said Rubinstein. "If we're going to get anywhere, we need to share data."

Dr. Wendy Rubinstein, NIH Genetic Testing Registry

Tantalizing Rewards

Molecular diagnostics have proven their value in many ways, but innovation continues. New products could have a particularly dramatic impact on cancer, in which different mutations drive disease growth, metastasis and treatment resistance.

During *Gene Sequencing: Early Signal for Clinical Relevance,* Dr. Phil Febbo noted that, as sequencing costs come down and data processing power increases, clinicians will be motivated to sequence each patient's cancer, as well as their personal genomes. Dr. Febbo points to the Oncotype DX assay as an example of how molecular diagnostics can help physicians improve patient care.

"Patients with a low Oncotype DX score have less than a 10 percent chance of being treated with chemotherapy," said Dr. Febbo. "For patients with a high score, greater than 80 percent receive chemotherapy. If you're looking at utility, this is a very clear sign that physicians are listening to the test."

Equally important, NGS is identifying specific mutations that drive cancers and can be targeted for treatment. However, Dr. Febbo notes we do not always have the treatments to target dangerous mutations. More work needs to be done to expand our anti-cancer toolkit.

Understanding Mutations

Unfortunately, genetic mutations do not come with a big red tag that says DANGEROUS! Dr. James Ford discussed the challenges of assessing an individual's risk based on their genetics.

"There's the whole issue of variants of uncertain significance," said Dr. Ford. "These are changes in genes, but you can't predict the change will have a deleterious effect on the protein or that the change increases cancer risk."

Another issue is how patients should manage their own risk. Ford noted one patient, who had already been diagnosed with triple-negative breast cancer. A gene panel found she also had mutations for colon cancer, and a subsequent colonoscopy found and removed precancerous polyps.

On the other hand, genetic findings may not always be so clear-cut. Another woman had mutations for a dangerous form of stomach cancer, though she had no family history. Should she have her stomach removed as a safety precaution?

Laurie Levin, Cancer Survivor and Advocate

While Dr. Ford is optimistic about sequencing, he is also cautious. Results can be complex and are not always actionable. Patients can benefit with more precise diagnoses, but they can also be subject to unnecessary follow-up tests. To be effective, sequencing data must be put in the larger context of the patient's history.

Patients, the Ultimate Beneficiaries

It's easy to get caught up in the minutia of regulation, reimbursement and value. But at the end of the day, the goal is to help patients. To top off the Summit, cancer survivor Laurie Levin shared her story.

Levin has had a 38-year relationship with cancer. In 1977, at 28, she was diagnosed with non-Hodgkin's lymphoma, inoperable, stage 3B. She endured intense chemo and radiation, but the cancer was gone.

Fast forward to 2005. Levin found a lump in her breast, an area that had been irradiated in '77. But the previous cancer made her case more complicated. Chemo would be particularly risky, and she seriously considered a mastectomy instead of a lumpectomy.

What she needed was information, and she got it from the Oncotype DX. Her relatively low recurrence score cleared the way for a lumpectomy followed by radiation and hormone therapy—and no chemo.

"I am reminded how absolutely critical the Oncotype DX was to my recovery," said Levin. "It literally handed me my life back. Tests like these are life-changing events for any patient."

About California Healthcare Institute (CHI)

CHI represents more than 275 leading biotechnology, medical device, diagnostics and pharmaceutical companies, and public and private academic biomedical research organizations. CHI's mission is to advance biomedical research, investment, and innovation through effective advocacy of policies to improve public health and ensure the continued vitality of the life sciences sector. CHI's website is www.chi.org. Follow us on Twitter @calhealthcare, Facebook, LinkedIn and YouTube.

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