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CALIFORNIA HEALTHCARE INSTITUTE

A NEW ERA FOR DIAGNOSTICS

PERSONALIZED HEALTHCARE AND THE FUTURE OF MEDICINE

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A New Era for Diagnostics: Personalized Healthcare and the Future of Medicine

1. Executive Summary

The last decade has brought astounding advances in scientific understanding of biological information. New technologies generate flood of datas, providing the molecular diagnostics industry with a wealth of information to guide development of tests for everything from complex cancers to genetic diseases such as Alzheimer's, Huntington's and Parkinson's. As an example of how fast the molecular diagnostics industry has evolved, rapid tests for influenza can now produce results in just 15 minutes. To date, ten rapid flu tests have been approved by the U.S. Food and Drug Administration (FDA). New discoveries are happening every day, driving more advanced methods for diagnosis. Late last year, the World Health Organization hailed a new rapid test for tuberculosis (TB) that produced results in just two hours. This replaces the most common testing method for TB, known as the "smear test," which is more than 100 years old and relies on the human eye to look through a microscope and recognize the TB bacteria. With respect to drug development, companion diagnostics are changing the way drugs are made and marketed. Using a companion test to predict whether a drug will work in individual patients, or what level of dose that person should receive, has gained momentum in recent years, leading many health experts to predict that personalized medicine will eventually become the norm.

Scientific advancements like these, though, face barriers to adoption. Regulatory agencies such as the FDA have trouble keeping pace with the pace of science, which includes the discovery of new

biomarkers. (Biomarkers are an indicator of normal biological process. The presence of an antibody, for example, may indicate infection.) As an example, of the 40 or so drugs associated with diagnostic tests, the FDA requires a companion diagnostic to be used for only about five. While some drugs — such as the blood thinner warfarin — carry updated labels with recommendations to use a test, the majority have only updated information about the possible genetic link to side effects and optimal dose.

Another example of regulatory lag is in the area of personalized DNA testing, where laboratory-developed tests (LDTs) reveal information about an individual's propensity for diseases such as Parkinson's and breast cancer, and how that person may respond to common treatments such as the antiplatelet Plavix. This type of information proves useful for treating patients in an emergency setting, and sets the stage for individualized medicine with potential for cost savings and more efficient care.

Eventually, scientists say everyone will undergo whole genome testing as a part of their overall health assessment. Doctors trained specifically to deal with genetic health will be able to include this information as a part of the medical record, and assess an individual's health based on it.

First, however, the FDA must weigh whether personal DNA tests sold over the Internet are considered medical devices or educational tools. FDA guidance surrounding laboratory-developed tests could help these manufacturers navigate a complex regulatory environment. And California-based laboratories that perform genomic analysis, using an individual's saliva sample to analyze her genetic make-up, will require greater clarity on the standards state and federal health authorities impose.

Given an uncertain and dymanic regulatory environment for diagnostics, CHI convened a group of industry experts, policymakers and issues advocates Nov. 8, 2010 for "Keeping Pace with Technology: Molecular Diagnostics Regulation" held at Roche Diagnostics in Pleasanton, Calif. The day-long event explored implications for diagnostics moving forward, including changing regulatory pathways and the influence of public policy at the state and federal levels.

2. Setting the Stage

A sense of uncertainty prevails among diagnostics companies trying to introduce tests with potential to revolutionize human health. This, in part, is due to a lack of clear guidance from regulatory authorities. The FDA, under great scrutiny by lawmakers and consumer advocacy groups following some highly publicized adverse drug events, has been reluctant to provide guidance on pathways for approval of companion diagnostics and laboratory-developed tests.

In 2005, the agency issued a concept paper that outlined its thinking on Rx/Dx, or companion diagnostics, co-development. But a thorough review by drug and diagnostics companies concluded that the agency's proposed guidelines were too idealistic and failed to account for the challenges of aligning competing interests, separate drug and device development timelines and divergent regulatory pathways. Five years after that initial guidance was released, FDA Commissioner Margaret Hamburg told industry to expect updated guidance in late 2010, giving diagnostics companies hope that a clear policy would have the potential to streamline regulatory approval of companion devices. But late last year, the agency said that it would delay the process, extending the timeline into 2011.

Earlier that same year, the FDA announced its intention to regulate several direct-to-consumer (DTC) genetic tests as medical devices, a clear divergence from industry opinion that the tests serve as an educational tool rather than a diagnostic designed to influence healthcare decision making. The House of Representatives Committee on Energy and Commerce, led by Chairman Henry Waxman, launched an investigation into DTC genetic testing companies in May 2010, sending letters to several prominent California-based companies, following the announcement by San Diego-based Pathway Genomics that it would sell DNA kits at Walgreen Co. stores nationwide. The congressional oversight came as a surprise to companies that had been selling the kits over the Internet for years.

In its letter addressed to the companies, the House committee requested information about the diseases tested,

policies concerning genetic counseling or physician consultation, data demonstrating accuracy of risk predictions and documents relating to the services' compliance with FDA regulation.

Walgreen's backed out of its plans with Pathway to sell the kits in its stores. Simultaneously, CVS/Caremark, which had also intended to sell the saliva sample collection kits in a similar deal later that year, put its plans on hold until regulatory issues were resolved.

Alberto Gutierrez, director of the FDA's Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), said that long before Pathway decided to extend its service from the Internet to store shelves, the agency had been in discussions with players in the DTC genomics industry. But the rules have been unclear and inconsistent, without a clear path for California's personalized genetics companies.

3. Policy Perspective: Regulation of Laboratory Developed Tests

Issue at a Glance:

Advances in technology and the proliferation of new genomic information is rapidly changing the commercial diagnostic landscape and opening up new opportunities for advanced diagnostic tests. Government policies will play a crucial role in diagnostic innovation and have the potential either to slow such innovation or to help lower diagnostic development risks and barriers, according to industry leaders who gathered for the CHI forum.

Also at risk for the diagnostic industry is venture funding, which sees regulatory barriers to approval as a major risk. Venture firms, already hard hit by the recession and unable to raise funds as they have in the past, could divest their interests in molecular diagnostics if the FDA placed new barriers to approval in their pathway. Venture investors are also concerned about reimbursement. Without a clear source of payment for diagnostic products, investors will exercise caution in funding these innovative new technologies.

> **"Everybody is looking for** a regulatory framework that will lead to clinical claims that are useful for physicians"
>
> *Dr. Paul Radensky,*
> *Partner, McDermott Will & Emery LLP*

Highlights of the discussion included:

- Attorneys and industry investors say the diagnostics industry is bracing for an onslaught of new customers due to the passage of healthcare reform legislation, which could bring as many as 30 million uninsured individuals into the healthcare system. The challenge, according to Kleiner Perkins Caufield & Byers venture partner Risa Stack, is, "How do you get the right treatment to the right patient at the right time?"
- Stack also spoke of a new initiative dedicated to advancing diagnostics that would personalize care and lower costs. The Coalition for 21st Century Medicine has worked with the FDA on specific guidance impacting the diagnostics community along with educating policymakers about the importance of innovative molecular diagnostics and personalized medicine.
- Mark Gudiksen, vice president of TPG Growth LLC, highlighted some of the most innovative companies in the TPG Growth portfolio, such as Nodality, which is characterizing the molecular basis of diseases. The Stanford University spinoff helps pharmaceutical companies and doctors better understand why individuals respond differently to drugs and how to design the most effective treatments for them.
- Garret Hampton, senior director of oncology biomarker development at Genentech, highlighted the company's 2008 citizen's petition, which called for agency regulation of all in vitro diagnostic tests intended for use in drug or biologic therapeutic decision making. Such a rule would hold all such tests to the same scientific and regulatory standards.

Clinical Laboratory Improvement Amendments (CLIA)

- Congress passed the Clinical Laboratory Improvement Amendments (CLIA) in 1988 establishing quality standards for all laboratory testing to ensure the accuracy, reliability and timeliness of patients' test results regardless of where the tests were performed.
- A laboratory is any facility that performs testing on specimens derived from humans to give information for the diagnosis, prevention, treatment of disease, or impairment of, or assessment of health.
- CLIA is user fee funded; therefore, regulated facilities cover all the costs of administering the program.
- Centers for Medicare & Medicaid Services (CMS) assumes primary responsibility for financial management operations of the CLIA program.
- The categorization of commercially marketed in vitro diagnostic tests under CLIA is the responsibility of the FDA. This categorization includes the process of assigning commercially marketed in vitro diagnostic test systems to one of three CLIA regulatory categories based on their potential for risk to public health:
  - o waived tests
  - o tests of moderate complexity
  - o tests of high complexity
- CLIA categorizations will also be announced in Federal Register Notices, which will provide opportunity for comment on the decision. FDA may reevaluate and recategorize these tests based upon the comments received in response to the Federal Register Notices.
- FDA will revise as necessary criteria for waivers, moderate and high complexities.

U.S. Food, Drug and Cosmetic Act

The U.S. Food, Drug and Cosmetic Act is a set of laws originally passed by Congress in 1938 giving authority to the FDA to oversee the safety of food, drugs and cosmetics. It replaced the earlier Pure Food and Drug Act of 1906 and for the first time gave FDA authority to regulate medical products.

Source: FDA

Expert Opinions:

While the FDA had historically declined to regulate LDTs, the introduction of DTC genetic tests sparked the agency's interest. In 2007, the modern era of personalized genetic testing was born with the launch of DTC products from the publicly-traded deCODE Genetics and the Google-backed 23andMe.

With 23andMe, deCODE and, soon to follow, Navigenics, consumers could now pay $1,000 to receive information about their genetic makeup, including ancestry, drug response and propensity for disease, characterized by most as low, medium or high risk.

Following the launch of Knome in late 2007, consumers could also pay much more ($350,000) to review their entire genetic makeup. Despite the introduction of products that would shift the DTC product landscape, the legal landscape remained essentially unchanged. Regulatory oversight was still rarely invoked and remained confusing to companies.

At the federal level, while most DTC genetic tests were likely covered from the outset by Clinical Laboratory Improvement Amendments of 1988 (see chart), it was typically difficult to determine whether DTC genetic testing companies were operating using CLIA-certified labs.

According to Danelle Miller, a global quality and regulatory affairs attorney with Roche Diagnostics, the FDA has been struggling for some time with the dual regulatory paradigm between CLIA laboratories and

commercial IVDs, which fall under FDA purview of the federal Food, Drug and Cosmetic Act (see chart).

The FDA has, at times, considered plans to strengthen oversight of laboratory-developed tests by reopening its 1997 analyte-specific reagent, or ASR, rule. ASR rules allow CLIA-certified clinical laboratories to use ASRs as individual building blocks for developing genetic assays and other kinds of tests. Laboratories are required to develop and maintain the test's analytical (but not clinical) performance. They also must report test results with the boilerplate disclaimer: "This test was developed and its performance characteristics determined by [laboratory name]. It has not been cleared or approved by the FDA."

Under the ASR rule, test manufacturers are not required to seek FDA premarket approval for low-risk (Class 1) ASRs, which consist primarily of the active ingredients for genetic tests. To qualify for the regulatory exemption, the manufacturer cannot make analytical performance or clinical claims for the ASR. Nor can it provide clinical labs with instructions on how to use the ASR.

In July 2010, the FDA held a public meeting to gather input from stakeholders to help guide its plans for regulating lab-developed tests (LDTs). The agency closed its comment period in September, and is in the process of reviewing the feedback.

Sheri Hall, vice president of quality and regulatory affairs for Becton, Dickinson and Co., said BD supported the concept of listing various tests and the clinical laboratories involved "so that would help the agency at least get their arms around the size and magnitude of the number of providers of these types of tests."

Liz Lison, a regulatory and compliance consultant with Advocea LLC, said she proposed a type of third-party authorization that would validate the biomarkers in question to keep clinical labs from bringing an "out-of-control" test to market.

Lison said many laboratories she was working with found the systems involved in preparing for FDA and CLIA regulations very different from one another.

"Both quality systems serve the same purpose; they're both there for safety and effectiveness," she said. "The problem is that they're divided by common language; many of the words in one quality system mean something completely different in the second one."

Genentech's Hampton stressed the importance of regulating laboratory-developed tests so that doctors can rest assured they are making treatment decisions based on sound science.

"When Genentech identifies a biomarker that we believe predicts a patient efficacy or lack of efficacy we're held to an incredibly high standard in terms of determining the validity of that claim," he said. "We believe that for high-risk LDTs, the same standard should apply."

Meanwhile, California health officials have begun working with DTC genetic testing companies to help them achieve state licensure, according to Kathy Williams, an examiner with the California Department of Public Health's Laboratory Field Services. Navigenics and 23andMe, for example, have been licensed along with many others.

"Our mission is to protect the health and welfare of the citizens of California by ensuring accurate, precise and reliable laboratory test results," she said. "It's been quoted many times that 80 percent of medical decisions are based on laboratory results."

4. The Future of Personalized Medicine: Next Generation Sequencing and Diagnostics

Issue at a Glance:

Since the completion of the Human Genome Project in 2003, the scientific community has deepened its understanding of the genetic basis for disease. We now know, for instance, about the principal genes connected to the muscle inflammation side effects of statins, the response to interferon therapy for hepatitis C and the liver

side effects of antibiotics like flucloxacillin. Our knowledge about pharmacogenomics — the interaction of genes with drugs — is exploding, and this area now represents one of the biggest advances since the Human Genome Project.

> **"If you Googled personalized healthcare five years ago,** you'd get a couple of companies that would have hits. If you do it today, I would guess that most of us represented in this room would come up with a hit with personalized health care. Is this a trend or is this something that really can drive value for our industry?"
>
> *Neil Gunn*
> *Vice President of Global Diagnostics,*
> *Roche Molecular Diagnostics*

At the same time, many of these advances have outpaced knowledge in the medical community, where, traditionally, physicians have not been trained in interpreting genetic information. Meanwhile, genetic sequencing technologies have progressed swiftly, and many predict a future when whole genome sequencing is as common and routine as the physical exam.

Expert Opinions:

As we enter this new era of understanding surrounding the human genome, researchers envision a future where medicines are tailored to individuals, minimizing side effects and maximizing efficacy.

Three major forces are contributing to the advancement of personalized medicine, according to Peter Maag, global head of diagnostics with Novartis Diagnostics. First and foremost is access to genomic information, which has become easier, with technological advances driving more data into smaller and smaller machines. These so-called "gene machines" have been put into practice around the world, most notably by the Beijing Genomics Institute, which has invested in numerous systems made by San Diego-based Illumina. Greg Heath, senior vice president and general manager of Illumina's diagnostics business,

Glossary of Diagnostic Industry Terms

510(k): Premarket notification for most devices; named for the section of the law that requires these submissions

CDPH: California Department of Public Health

CDRH: Center for Devices and Radiological Health; FDA center in charge of medical device regulation

CE Mark: Symbol representing compliance with a European device directive; products bearing a CE mark may be sold in the EU

CGMs: Continuous Glucose Monitors; used in diabetes care

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

GINA: Genetic Information Non-Discrimination Act of 2008; protects Americans from discrimination based on their genetic information when it comes to health insurance and employment

HIPPA: Health Insurance Portability and Accountability Act; one section of the law that protects patient medical information from disclosure

IDE: Investigational Device Exemption; An IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to FDA.

IVDs: In vitro diagnostics; tests conducted outside of the body, usually in a laboratory

IOM: Institute of Medicine; advisor to the nation on health

ISO: International Standards Organization; group that develops voluntary standards for many types of products

ISO 13485: Medical Devices – Quality Management Systems – Requirements for regulatory purposes; used in Europe (and with additions in Canada) to ensure safe devices; current version published in 2003

ISO 14971: Medical Devices – Application of risk management to medical devices; standard used in many parts of the world to assess device risks; current version published in 2007

LDTs: Laboratory-developed tests

MDUFMA: Medical Device User Fee and Modernization Act; MDUFMA amends the Federal Food, Drug and Cosmetic (FFD&C) Act to provide FDA important new responsibilities, resources, and challenges. MDUFMA has three particularly significant provisions:

- User fees for premarket reviews;
- Establishment inspections may be conducted by accredited persons (third-parties);
- New regulatory requirements for reprocessed single-use devices.

Misbranded: FDA term used to describe products whose information is false, misleading, missing, or lacking in prominence, or whose packaging is misleading or improper

NDA: New drug application

PDUFA: Prescription Drug User Fee Act; A law passed by Congress in 1992 which allowed the FDA to collect fees from drug manufacturers to fund the new drug approval process.

PMA: Pre-market approval application

Premarket notification: See 510(k)

said the company can now run two genomes at 30x coverage in a week, approximately the output of the entire (13?) human genome project(s) in a day.

The second factor is a greater understanding of biological pathways. This has been improved through the abundance of biomarkers, or molecular-level indicators that a drug is working. Biomarker discovery is also helping to guide predictive patterns of disease, particularly for areas of complex diseases such as cancer.

> **"As prices get lower and lower,** more and more applications are going to be used for next-generation sequencing."
>
> *Greg Heath*
> *Senior Vice President and General Manager of Illumina's Diagnostics Business*

Finally, demand for rational data to inform clinical decision-making provides diagnostics companies with ripe opportunity for growth. First, however, companies must navigate questions such as, "What determines clinical validity?"

Highlights of the discussion included:

- John West, CEO of ViaCyte, shared with the audience his own experience with genetic testing. West and his family received interesting insights about their ability to metabolize certain drugs, such as those for treating acid reflux, and other risk factors. "So far, whole genome sequencing has yielded medically actionable results for our family and we expect that to grow," he said.
- Eric Lai, senior vice president of research and development at Gen-Probe, spoke of the company's increasing interest in next-generation sequencing technologies, most recently with its investment in Pacific Biosciences of Menlo Park.
- Mitch Nelles, vice president of research and development and technical operations of XDx, provided some insight as to how the industry might transition some of these technologies into the diagnostics environment.
- Tina Hambuch, scientific liaison for Illumina's Clinical Services business and education coordinator and director of its Clinical Genetic Molecular Biologist Scientist training program, weighed the implications of providing clinical assessments to the physician community.

Conclusion

New biological discoveries have contributed to major advances in the diagnostics industry. New biomarkers and cheaper, faster genetic sequencing tools are fueling growth and contributing to ever greater knowledge surrounding complex diseases like cancer. As the industry continues to grow, though, science is outpacing the regulatory environment, and many companies are left without clear guidance from the FDA. As the agency considers regulation of laboratory-developed tests, it is important that it keeps clarity and consistency in mind.

Partnering with CHI

CHI-California Healthcare Institute is working to ensure that any new regulatory action takes into account the views and perspectives of California's innovative diagnostics sector, so that changes to the regulatory pathway should promote predictability and consistency in the process, and not, without sound justification, add additional requirements or burdens to the detriment of medical technology investment and innovation. CHI welcomes your participation in future discussions on the regulatory environment and medical device innovation. Contact Todd Gillenwater, senior vice president of public policy for CHI, at 202-974-6313 or gillenwater@chi.org for more information on how to get involved, or visit the CHI website at www.chi.org.

Resources

FDA Office of In Vitro Diagnostics (OIVD):
http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm

California Department of Public Health (CDPH) Laboratory Field Services:
http://www.cdph.ca.gov/programs/lfs/Pages/default.aspx

July 22, 2010 Congressional Hearing: Direct-To-Consumer Genetic Testing and the Consequences to the Public Health:
http://energycommerce.house.gov/index.php?option=com_content&view=article&id=2083:hearing-on-direct-to-consumer-genetic-testing-and-the-consequences-to-the-public-health&catid=133:subcommittee-on-oversight-and-investigations&Itemid=73

AdvaMed 510(k) action/opinion:
http://www.advamed.org/MemberPortal/Issues/FDA/

Medical Device Manufacturers Association 510(k) action/opinion:
http://www.medicaldevices.org/issues/FDA

CALIFORNIA HEALTHCARE INSTITUTE

Headquarters
888 Prospect Street, Suite 220
La Jolla, California 92037
858-551-6677
858-551-6688 fax

Sacramento
1215 K Street, Suite 940
Sacramento, California 95814
916-233-3497
916-233-3498 fax

Washington, D.C.
1608 Rhode Island Avenue, NW,
Room 238
Washington, D.C. 20036
202-974-6300
202-974-6330 fax

www.chi.org