G2 INTELLIGENCE

Diagnostic Testing & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

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Personal Genome Interpretation Now Offered on Smartphones as Diagnostics Apps Penetrate Market

Accessing and understanding one's own genetic information is now just a push of a smartphone button away. The smartphone app GeneG allows users to browse their genome. Such apps are part of a larger trend of bringing access to laboratory tests and test results directly to patients through mobile technology platforms.

GeneG was created by Noam Shomron, Ph.D., from Tel Aviv University (Israel) and allows individuals to upload their whole-genome sequencing data to a Web site for analysis, with results available on mobile devices. Identified genomic variations will be displayed and linked to databases such as PharmGKB database for sensitivity to drugs and genomewide association studies for predicting genetic diseases. As new analytical tests are developed, they are integrated into software updates, and users can apply them for updated analysis of their genome right away.

"If we give this power to the general public, it will put pressure on the medical field to catch up with this information," Shomron says in a statement. He believes having this data easily accessible will advance the adoption of personalized genomics, particularly pharmacogenomics.

For more on development of mobile health apps and their regulation, please see the special focus section beginning on page 9.

In Tough Reimbursement Climate the Promise of Value-Based Pricing Harder to Realize

Specialized laboratories are caught in a catch-22. Value-based pricing of tests remains an alluring economic salvation, but in an environment in which reimbursement for previously covered tests is not guaranteed, value-based pricing models are being skeptically examined by payers intent on reining in health care spending.

In the recently released white paper, *2013-2014: Evolving Challenges for Value-Priced LDTs*, Bruce Quinn M.D., Ph.D., a senior health policy specialist at the law firm Foley Hoag, re-examines the case for value-based pricing nearly 10 years after the influential launch of Oncotype DX (Genomic Health), which has been credited with changing the reimbursement landscape for novel diagnostics.

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"Working in a field that is dominated by commodity pricing, the value-based model is seen as a panacea by lab industry executives. . . . However, this model requires not only value pricing argumentation on paper, but a market monopoly in practice," writes Quinn. "My experience in watching the reactions of payer policymakers to value pricing economic models suggests that the value pricing scenario is often viewed by the listener as too artificial."

While heralded as a success, Oncotype DX took six years from the test's launch for the company to achieve profitability. The hope is that more recently launched tests will face a shorter road to profitability given the rapid signs of positive reimbursement decisions by major insurers for coverage of noninvasive, cell-free fetal DNA testing. However, the true economic success of recently launched value-based tests won't be realized for several years and the next crop of tests (including algorithmic, multi-analyte tests and next-generation sequencing-based tests) are likely to endure tough scrutiny in a payer landscape confounded by increased transparency with the new molecular pathology codes and failure of the Centers for Medicare and Medicaid Services to recognize the value of algorithmic tests beyond the sum of their component parts.

"Working in a field that is dominated by commodity pricing, the value-based model is seen as a panacea by lab industry executives. . . . However, this model requires not only value pricing argumentation on paper, but a market monopoly in practice."
—Bruce Quinn, M.D., Ph.D., Foley Hoag

Quinn highlights the fact that most emerging tests fall into a gray area of value-based scenarios, compared to the black-and-white scenarios lauded in textbook cases.

"It is rare that new tests address a clinical area where there is a dearth of information and in which the new test being developed promises to have a sole source position," Quinn explains. "More typically, the clinical scenario comprises multiple and uncertain patient presentations, heterogeneous patients, and multiple therapeutic choices, and the new information provided cannot be regarded as a 'monopoly' type of information that can be framed in only 'one' scenario for care (either X without our test or else Y with our test.)."

In truth, blockbuster advances in any area of medical technology are rare, and most advances are incremental, leading payers to be skeptical because some novel diagnostic tests that are brought to their attention have relatively little advantage over existing practice, Quinn says. Additionally, despite the claims of cost savings, it is rare for a test to truly be cost-saving. Usually, the test simply is proposed to have an "acceptable" cost-effectiveness ($40,000 per quality adjusted life year), which means it is actually cost-increasing for the payer.

From 2008 to the present, local Medicare contractors (particularly Palmetto GBA through its MolDX program) have been "early adopters" of these tests and have served as a great evidence base, but it remains to be seen whether this trend will continue, Quinn cautions.

"The question for labs in 2013 and in years forward is whether the bulk of the market will step up to coverage relatively quickly after local Medicare coverage (the conventional diffusion model) or else, whether Medicare LCD decisions will appear more as 'early adopter' actions that are followed by a 'chasm' that needs to be crossed using deliberate and different strategies," writes Quinn.

This potentially increasing chasm will be difficult for laboratories to bear as converting each individual adopter into general market acceptance will require a substantial number of individual hearings with insurers. Quinn cites the fact that it now takes over 50 individual payer registrations, relationships, and contracts (traditional Medicare, 38 Blue Cross Blue Shield plans, and up to 10 different Medicare Advantage plans) to access the same 150 million covered lives previously covered under a local Medicare contractor and the Blue Card.

The evidence that test developers must bring to these hearings is also highly disputable. Quinn says that while necessary, a dossier summarizing peer-reviewed publications is inherently viewed with skepticism because it is written by the company. Additionally, the evidence from technology assessments needed to win positive coverage is often biased against diagnostic tests since they are not evaluated in double-blind trials and survival may not be the best metric of tangible benefit. Companion diagnostic tests, which are studied in U.S. Food and Drug Administration trials for their corresponding drug candidate, are the most straightforward and often have the strongest evidence, while multianalyte tests reporting a single result based on an algorithm will be subject to greater scrutiny.

"Technological change is only accomplished when adventure and investment are repaid; that is, when market prices are above marginal cost," Quinn concludes. "Providing the appropriate, and hopefully socially optimal, repayment for the breakthroughs in molecular testing [is] a challenge that deserves to be faced head on."

Takeaway: While test developers are hopeful that value-based testing will win favor with payers, there will be increasing scrutiny of the evidence base to prove true cost savings to an increasingly fragmented payer market.

Surge in Life Science IPOs May Be Penetrating Diagnostics Market

Is the much-talked-about pop in initial public offerings (IPOs) among biotech companies reaching the diagnostics segment? After the highly watched public debut of Foundation Medicine (Cambridge, Mass.), industry watchers are hopeful that the answer is yes, but an examination of the evidence points to the fact that diagnostics companies have not fared as well as their pharmaceutical and other life sciences counterparts when entering the public markets.

More than three dozen biotech companies have filed for IPOs this year—a number experts say exceeds any other time in more than a decade. But according to life sciences financial services firm Burrill & Co. not all have been market successes. Of the 23 life sciences IPOs priced in the first half of the year, 10 launched below their target, with only two therapeutics companies priced above their target range. But from July through September, of the 16 IPOs that set pricing, only two completed

their offerings below their target ranges and five priced above their targets, including Foundation Medicine.

Foundation Medicine is the shining example of a diagnostics IPO success. The company raised about $106.2 million with its $18 per share IPO. In its first day of trading on Sept. 24 it was one of the most heavily traded stocks of the day, according to Reuters, and reached a high of $34.19 for the day, 89 percent above its offering price. In its first week of trading, the company's stock price rose another 12 percent above its first-day close but then has fallen with the market as a whole in light of concern over broader political and macroeconomic forces.

While skeptics look at the unprofitable company's IPO success as part of the hype of personalized medicine, Foundation Medicine's IPO is being looked at as a bellwether for other genomic-based diagnostics companies eager to raise capital in an environment of uncertain reimbursement prospects.

"There has been a fairly dramatic shift in the IPO market," Daniel Levine, managing editor of the *Burrill Report*, tells *DTET*. "Initially public companies had marketed products. Now earlier-stage companies are accessing the public markets" as public market investors have increased their risk appetite.

Following in Foundation Medicine's footsteps is CardioDx (Palo Alto, Calif.), which filed papers in October for an $86 million IPO. Back in September Veracyte (San Francisco), maker of the molecular Afirma thyroid test, filed plans for a $75 million IPO as did circulating tumor cell testing firm Biocept (San Diego), which filed for a $23 million raise.

"Companies are lining up to get their deals done as fast as possible as protracted dysfunction in Washington can disrupt momentum," Levine says. "But if you look at the companies that are successful they are able to tell a story and capture the imagination of investors. IPOs can get done in any environment."

Performance of U.S. Diagnostics IPOs in 2013

Company	IPO Date	Target Range	Offering Price	Price as of 9/30/13	Return from IPO
LipoScience	1/25/2013	13-15	9	5.00	-44.4%
Cancer Genetics	4/5/2013	11-13	10	20.26	102.6%
NanoString Technologies	6/25/13	13-15	10	11.00	10.0%
Foundation Medicine	9/24/13	14-16	18	39.64	120.2%

Source: Burrill & Co.

But not all diagnostics companies have been as successful in the IPO market this year as Foundation Medicine. NanoString Technologies (Seattle) had a tougher start in its June 25 public market debut with stocks dropping more than 19 percent below its already discounted offering price. Priced at $10 per share, below the targeted $13 to $15 per share, the shares closed the first day at $8.06, which according to the *Seattle Times* was the worst first-day results of any of the 151 offerings listed in Nasdaq's IPO database in the previous 12 months. As of Sept. 10 the share prices have remained above the asking price.

Takeaway: While the biotech IPO market is reaching levels unseen in the last decade, diagnostics companies have not all performed well, despite the optimistic start of Foundation Medicine.

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Inside the Diagnostics Industry

CellScape to Enter Noninvasive Prenatal Market With Whole Fetal Cell Microarray Test

Ted Snelgrove, CEO, CellScape

Karen Drexler, co-founder, CellScape

CellScape (Newark, Calif.) is poised to enter the rapidly growing noninvasive prenatal diagnostics market in the second half of 2014 with its Clarity Prenatal Test. Unlike other currently marketed tests, Clarity relies on whole fetal cells and targeted microarray technology to detect roughly 30 chromosomal abnormalities (microdeletion/insertion syndromes) beyond common aneuploidies (Trisomies 21, 18, and 13), making the tests' results capabilities the closest to invasive testing like amniocentesis, the gold standard, in terms of genetic coverage.

Acknowledging a competitive market space and reimbursement challenges, CellScape has strategically positioned itself with its patented fetal cell separation methodology, enabling the company to initially enter the market by partnering with existing reference and academic labs.

DTET recently spoke with CellScape's CEO Ted Snelgrove, who joined the company in July, and co-founder and executive chair Karen Drexler regarding the development and launch of Clarity as well as the future of noninvasive prenatal testing.

What differentiates CellScape's approach from other companies' in the noninvasive testing space?

Drexler: We had looked at the other approaches and what everybody else had attempted to do in this field. Because our team is an engineering team, rather than out of traditional biology, we took a very different approach. The standard techniques available in labs—various molecular enrichment techniques, magnetic cell sorting, and fluorescent cell sorting—have the goal to reduce down the population of cells from 100 billion cells, which you have in two tubes of blood. Everybody else tried to get down to 1 million to 3 million cells, which is about what you can view on one or two or three microscope slides. We, however, decided we wanted to maximize retention of nucleated cells, which have DNA.

In our first enrichment step, we only eliminate non-nucleated red blood cells. At the end of our enrichment process, which is a proprietary process, we are left with about a billion cells. Using advances in hardware and software, tools that are more often used for defect recognition, like on silicon wafers, we are able to isolate cells of interest through these optical techniques versus using physical cell separation. It has really made a difference.

Why did CellScape choose to use microarray technology rather than next-generation sequencing?

Drexler: We are a sample prep company primarily. Our goal is to retain high-quality fetal cells that can be applied to whatever kind of genetic analysis is most appropriate. That is what we do uniquely. We initially thought we would use fluorescence in situ hybridization (FISH) because the market was addressing whole-chromosome abnormalities and we could visualize and count whole chromosomes beautifully with FISH. The key driver of our decision to move to microarray was Ronald Wapner's NIH [National Institutes of Health]-funded study. That study proved that you could identify a large number of additional pathogenic, important disorders in

utero by using chromosomal microarrays versus karyotype. Dr. Wapner presented his findings in February 2012 and culminated in a series of articles published in the *New England Journal of Medicine* in December 2012. Once the data was published, it was evident that microarrays would become the gold standard in the marketplace.

We decided to go to the market with a genetic analysis method that was proven, that was understood by physicians and genetic counselors, and that would be used as the standard for detecting a broad range of genetic abnormalities. We will enter the market with a change in sample—using a needle in the mother's arm rather than a needle in her belly to draw fluid containing fetal cells. At leading labs around the country, chromosomal microarrays either are or are becoming the standard of care. We want to leverage that movement in the market and launch with a novel approach to the sample, but not with changes in the method with respect to the analytical testing.

We also studied sequencing and we do not believe sequencing is the best method today for looking at a large number of copy number variants. It has been done in academic settings, but it costs too much and takes too long to be practical for commercial testing at this time. And the market is not familiar with sequending for prenatal genetic syndromes. Our work in terms of test validation is a lot easier with microarrays and the market understands the use of chromosomal microarrays to assess copy number variants.

"We decided to go to the market with a genetic analysis method that was proven, that was understood by physicians and genetic counselors, and that would be used as the standard for detecting a broad range of genetic abnormalities. We will enter the market with a change in sample—using a needle in the mother's arm rather than a needle in her belly to draw fluid containing fetal cells."
—Karen Drexler

What is the process by which CellScape will decide to add a variant to Clarity?

Drexler: This is an area where we want to follow what the market had decided, as opposed to leading the market. We want to incorporate elements into our test that the industry agrees should be tested for prenatally. We are looking to outside experts to help us make those decisions. We have not finalized design of our commercial array yet, but the process we have used is very, very thorough. We started out with all of the data from the Wapner study—all of the chromosomal microarray findings—and looked at those things with pathogenic connections. We are using a targeted microarray that focuses for development purposes on the 30 or so most prevalent defects that are highly penetrant and are very serious affecting the quality of life in the first couple years of life. We are not looking at genetic findings that are associated with disease later in life. We are not looking at traits that are not associated with poor health outcomes. We are only looking at genetic syndromes in which there is a significant impact early on.

We started with the Wapner study data. A geneticist on our team compiled a detailed summary syndrome by syndrome to get the best understanding of the impact of each condition and help us rank order the most serious ones for us to prioritize. We focused on those well-characterized genetic conditions where there is consensus among industry leadership about testing prenatally.

We expect that relevant scientific societies, like ACMG (American College of Medical Genetics), will come out with recommendations on these issues. We are

trying to be conservative in this regard. In addition, we just kicked off quantitative market research. We are looking to understand which genetic findings physicians are comfortable counseling patients on. We are working to combine published information and what industry associations designate with clinician input.

On the business side, noninvasive prenatal testing is a competitive marketplace. How is the company positioning itself strategically ahead of launch?

Snelgrove: Since 2001 I've been in the broader field of advanced molecular diagnostics. My emphasis has been building strong products with great brand equity that have become reference points in their medical specialties where they were developed—in oncology with Oncotype DX (Genomic Health) and in rheumatology with Vectra DA (Crescendo Bioscience). There is a great opportunity with the Clarity system to build a new brand and to do so at the high end of the market in terms of value proposition. I think there is an opportunity to come in and help define a market like this as noninvasive prenatal genetic testing is still in an early stage. CellScape will enter the market as a follower in the sense that there are marketed services already in this market. However, they all rely on cell-free DNA. From another perspective we are also a first mover because we will introduce noninvasive testing with a whole-cell approach. We are a hybrid in that regard.

CellScape By-the-Numbers

- 36 Employees in Newark, California
- 1 patent received and 8 pending
- 4 million live births each year in the U.S.
- 2.5 percent affected with abnormal diagnosis
- 1 in 60 pregnancies affected with a clinically relevant copy number variant

As this market matures, it has the potential to grow to 4 million tests per year in the United States alone, and it is potentially much larger than that if you look at the rest of the developed world. Segments may emerge over time. There will be an opportunity for Clairty to become the preferred choice for those who want to get as close to amniocentesis as possible, without having to undergo an invasive procedure. The goal will be to replicate the information from an amnio as much as possible without the risk. That's a somewhat different value proposition than other companies have and it will differentiate Clarity.

Reimbursement remains an issue throughout the noninvasive prenatal testing market. How do you see reimbursement impacting further adoption?

Snelgrove: We are sorting out the degree to which the advent of the new exchanges will change the market. Medicaid currently pays for a large share—nearly half—of all maternity care in the United States. As the Affordable Care Act is rolled out and the market reaches a new equilibrium, with some groups shifting to expanded Medicaid coverage, the reimbursement landscape will change. It is an open question at the moment that hasn't been resolved, but over time, I believe, any payer, including the governmental bodies with responsibility for these programs, will agree to provide access to genetic testing for all women who are pregnant, not just those of advanced maternal age, given the real risks for genetic abnormalities across all pregnancies.

The reason adoption was so fast for cell-free testing and the reason reimbursement happened so much more quickly than for any other diagnostic market in recent history is because of strong interest among the women themselves. There is more of a willingness to pay at the patient level than in any other market I've seen. While I am not expecting this in the long term to be a patient-paid service, it still means a lot that patients believe it should be covered.

Smartphones Expected to Bring Diagnostics To the Patients' Fingertips

Integrating the use of mobile devices such as smartphones and tablets into clinical care, or mobile health (mHealth), has the potential to transform the practice of medicine, allowing for monitoring of remote patients and encouraging a significantly more active role for patients in their own health care. Experts envision mHealth will drive an evolution of the health care system that will include real-time, decentralized monitoring of chronic conditions, as well as the ability of patients to run remote diagnostics off of their mobile devices.

"We are moving towards an ambient mode where information is constantly aggregated and insight from this will be constantly accessible. We are seeing a democratized framework for health care."
—Joe Smith, M.D., Ph.D., West Health

Mobile applications that allow for better management of chronic conditions through the automatic logging and transmission of testing results to health care providers are already in use, and the U.S. Food and Drug Administration (FDA) recently released its final guidance on the regulation of medical apps. This is a move the mHealth industry applauds, saying it adds needed clarity as to what apps are in fact medical devices and it should hasten development and adoption of mobile health apps, including those for diagnostic purposes.

The Future of mHealth

The potential of diagnostic apps is limited only by how well the data they generate are integrated into clinical workflow. Some experts envision a day where the combination of mobile phone cameras, sensors, and cloud computing will allow patients to run a gamut of basic laboratory tests right from their smart devices, allowing patients to not only access their health information for better wellness management, but also increasingly generate the data needed for clinical decisionmaking. Continuous, real-time health readings will supply care providers with improved insight, instead of just single point-in-time measurements obtained in traditional outpatient care.

"We are getting away from diagnosis as something you go to to get and away from [results] being something someone else has information about," Joe Smith, M.D., Ph.D., chief medical officer of applied medical research organization West Health, tells *DTET*.

The FDA Is Cracking Down

Well before the publication of its final guidance, the FDA sent a letter to Biosense Technologies (India), questioning the company's lack of clearance for its marketed uChek smartphone-enabled urinalysis system. uChek is a kit that allows cellphone cameras to read color differences on urine test strips, indicating unhealthy levels of protein and other substances in urine.

"Though the types of urinalysis dipsticks you reference for use with your application are cleared, they are only cleared when interpreted by direct visual reading. Since your app allows a mobile phone to analyze the dipsticks, the phone and device as a whole functions as an automated strip reader," the FDA wrote. "When these dipsticks are read by an automated strip reader, the dipsticks require new clearance as part of the test system."

The company has since ceased selling the app in the United States.

"We are moving towards an ambient mode where information is constantly aggregated and insight from this will be constantly accessible. We are seeing a democratized framework for health care. Baby boomers, as patients, are not OK with the system of doctors and offices and regulators acting as gatekeepers. They are interested in access to information themselves."

"Apps will move from a nicety to a necessity. . . . Health care has always been behind other industries, but other conservative markets like financial services are employing mobile apps to empower consumers. This will happen in health care too."
—Drew Hickerson, Happtique

Rapid growth of mHealth adoption is expected to continue worldwide. A widely quoted March report by mobile device consultants Research2Guidance says that the mobile health market may reach $26 billion by 2017 and that 500 million smartphone users worldwide will be using a health care app by 2015. Estimates vary, but industry experts believe that there are close to 50,000 mobile health applications currently available for purchase in app stores, including medical apps as well as fitness and nutrition guidance and tracking. However, increasingly mHealth products are emerging that actually turn a smartphone or tablet into a medical device capable of performing electrocardiography (ECG) monitoring, urinalysis, and blood-based infectious disease diagnosis and tracking.

"Everybody recognizes mobile is reality. Apps will move from a nicety to a necessity," says Drew Hickerson, assistant general counsel and senior director of business development at Happtique, a mobile distribution platform that enables discovery and display of health apps and digital content for health care providers. "Even today people leave home without their wallets, but not their mobile phones. Apps are convenient, approachable, and increasingly used for everything from ordering groceries to managing finances. Health care has always been behind other industries, but other conservative markets like financial services are employing mobile apps to empower consumers. This will happen in health care too."

mHealth Regulation and the FDA

Providers and developers have been seeking clarification as to what mobile apps are considered medical devices and are subject to regulation. The FDA released its final guidance in late September and said that it will only regulate a small portion of the vast number of mobile health apps. The guidance indicates the FDA intends to take a tailored, risk-based approach in which it will exercise enforcement discretion (meaning it will not enforce its authority) for mobile apps that pose minimal risk to consumers, such as those that merely allow patients to log test results but do not provide specific treatment or treatment suggestions.

"This is a classic case of what's old is new again," says Chris Bergstrom, chief strategy and commercial officer at WellDoc, an mHealth developer of BlueStar, an FDA cleared prescription-based platform that provides real-time coaching

to patients with type 2 diabetes. "The published guidance is consistent with the long-standing polices of regulated medical devices, even before the terms *mHealth* and *digital health* came to be. Meaning if a mobile product diagnoses, treats, or mitigates a disease or is an accessory to a medical device then it will be regulated. In other words, no surprises."

The FDA will focus its regulatory oversight on a subset of mobile medical apps that present a greater risk to patients if they do not work as intended. These apps fall into two categories—those that are used as an *accessory* to a regulated medical device (connects to such a device "for purposes of controlling the device(s) or displaying, storing, analyzing, or transmitting patient-specific medical device data") and those that *transform* a mobile platform into a regulated medical device (an app that turns a smartphone into an ECG machine or attachment of a blood glucose strip reader). These regulated apps will be reviewed using the same regulatory standards and approaches as traditional devices.

"Mobility is a platform, a mode of delivery. Regulation is of functionality, not the delivery mechanism," explains Kim Tyrrell-Knott, an attorney with Epstein Becker Green. "The guidance clarifies what is regulated. It is a first step. Now there will still be other challenges. How do you go through market clearance or approval? What data is needed to establish substantial equivalence for 510K? There are other issues and questions that now need to be addressed about making the processes and procedures as efficient as possible."

Still, the reaction from the mHealth community and venture capital community has been positive. Stakeholders have praised the FDA for a "user-friendly guidance" that provides specific examples.

"The guidance is a solid win for the industry, an accelerator if for no other reason than uncertainty has been reduced," predicts Bergstrom. "Specifically, long-term adoption of mobile health products will improve because the FDA

Mobile Diagnostic Apps Top Nokia Sensing XCHALLENGE

The Nokia Sensing XCHALLENGE is a $2.25 million global competition to accelerate the use of both hardware sensors and software sensing technology to improve health and well-being as part of a "mobile health revolution." The pool of 26 teams from seven countries was narrowed this summer to 12 finalists.

In October the Nanobiosym Health RADAR team (Boston) was awarded the competition's $525,000 grand prize. Its device enables diagnostic testing in the palm of your hand, unlike today's technology that requires a full diagnostic laboratory. The Gene-RADAR platform analyzes a drop of blood, saliva, or other body fluid placed on a nanochip and inserted into a mobile device, which then detects the presence or absence of a disease's pathogen in less than an hour. Nanobiosym has already demonstrated custom applications for E. coli and HIV/AIDS, with potential applications across the entire spectrum of health care, including diagnosis, monitoring, drug development, companion diagnostics, and personalized nanomedicine.

Distinguished award winners ($120,000 prize) also highlighted mobile diagnostic technologies, including MoboSens (Urbana, Ill.), which has a smartphone-based sensor that reports on the presence of chemical contaminants and bacteria in water and biofluids, and Silicon BioDevices (Palo Alto, Calif.), whose sensor diagnoses and transmits results from a finger-stick blood sample to mobile devices or electronic medical record systems.

has helped draw brighter lines, enabling patients and providers and investors to know which side of the line a product stands on—shown to be safe and effective or nonregulated."

A Changing Delivery System Expected to Be Receptive

While provider preferences are often cited as a challenge to market penetration of new technology, changes in reimbursement structures may actually incent greater use of mobile health products.

"Change is afoot throughout the whole system," Smith says. "Hospitals realize under health care reform that they don't just take care of patients in their walls. . . . They are all getting prepared for an ambient health care system with customer centricity. Labs are developing ways to help patients do point-of-care testing. It is easier to move data than it is to move the patient."

> ***"There are two camps in health care—those that believe health care will always be inefficient, inconvenient, and stuck in the dark ages and those who are optimistic that . . . we can leverage technology to radically transform the quality and efficiency of health care delivery. Mobile health is the embodiment of this camp."***
>
> ***—Chris Bergstrom, WellDoc***

In a system fostering interconnectedness and incented to provide the highest quality of care at the least cost, reimbursement for utilization of mobile health becomes less of an issue.

"In a fee-for-service-driven clinical environment, the question is who pays. But in an ACO world, it is suddenly quite advantageous," says Ben Crocker, M.D., from Massachusetts General Hospital's Ambulatory Practice of the Future. "If I can get information that is more accurate in a more timely manner, and it will lead to better outcomes, then ACOs will adopt mobile technology."

Still, Paul Rubin, a Washington, D.C.-based life sciences partner at law firm Ropes & Gray, cautions health care professionals to review the guidance from a liability perspective. "Now that the guidance has been finalized, the use or recommendation of those types of apps, in the absence of FDA approval or clearance, could create potential liability for health care professionals and providers—particularly if an app malfunctions or does not operate as intended, thus jeopardizing patient health."

The greater challenge facing providers, however, is ensuring that increasing sources of patient health data are interconnected in an efficient manner.

"There are two camps in health care—those that believe health care will always be inefficient, inconvenient, and stuck in the dark ages and those who are optimistic that just like every other industry from financial services to media/entertainment, we can leverage technology to radically transform the quality and efficiency of health care delivery," says Bergstrom. "Mobile health is the embodiment of this camp."

Takeaway: Diagnostic mobile technology will further penetrate clinical workflow as a result of both patient interest and systemwide financial incentives to more closely monitor remote patients.

Autism Research Community Enraged About Upcoming Release of Predictive Test

At best the test has been called "premature." Others have suggested the test is "misleading," built on "shaky data," and will be inappropriately marketed to a desperately worried and motivated group of women.

The test at the center of this firestorm is the MAR Autism test (Maternal Autoantibody-Related) developed by Pediatric Bioscience (PB; Sacramento, Calif.). The company, which declined a request to speak to *DTET*, claims MAR is "an informational test which determines if an individual has an increased chance of having a child with autism" and is intended for use as "a family planning tool" in women of child-bearing age who have already had a child with autism and child-bearing women over the age of 30 years, as well as in women of children 12 months to 24 months seeking a diagnosis for their child's developmental delay. The test, the company says on its Web site, currently measures eight specific autoantibodies specific to fetal brain proteins that have been linked to the MAR form of autism.

The test, which is expected to be commercially available in the second half of 2014, is based on work by a group of University of California, Davis researchers, including Judy Van de Water, Ph.D., who is chief scientific adviser to PB and licensed the patented antibody screening to the company. Their study, published in *Translational Psychiatry* this past July, says reactivity in a panel of antigen markers (lactate dehydrogenase A and B, cypin, stress-induced phosphoprotein 1, collapsin response mediator proteins 1 and 2, and Y-box-binding protein provides "99 percent specificity" of MAR autism risk.

> ***"Folks affected by autism are desperate for an early identifier because early treatment makes a difference, but we are just not there yet."***
> ***—Tom Wassink, M.D.***

A slew of autism experts publicly dispute these findings, including in a news piece published in *Science* on Sept. 13. In addition to some skepticism about the suggested mechanism by which a direct antigen–antibody interaction inside the blood-brain barrier causes functional interference of the target proteins, researchers point to the study's small sample size, lack of independent validation of the markers, and "weak" statistical analysis used to derive the study's claims.

The study concluded that nearly 23 percent of the 246 mothers of children with autism tested had one of the "specific combinations" of autoantibodies against the target proteins. Critics say that combining reactivity patterns, none of which were seen in more than 7 percent of mothers tested, exaggerates the test's predictiveness. Steven Goodman, M.D., Ph.D., a clinical trial expert and Stanford University biostatistician, calculated for the Science article that the test has an actual positive predictive value (PPV) of 16.5 percent (meaning that only one out of six positive tests would be correct) and calls the company's claim that a woman with a positive test has a 99 percent likelihood of having a child with autism "completely false."

"Seventy-seven percent of the time the test will miss a positive case and a positive test will be wrong 83 percent of the time—it is really bad both coming and going," George Anderson, Ph.D., an autism researcher at Yale University tells *DTET*. Anderson adds

that there are other problematic autism tests emerging, including one that uses placental tissue, and despite the hope of a reliable test, the heterogeneous nature of autism spectrum disorder and its relatively low prevalence makes test development challenging.

While it is tempting to be able to identify a specific cause or risk factor for autism (currently only 10 percent to 20 percent of cases can be tied to a wide variety of genetic mutations), Tom Wassink, M.D., from University of Iowa, tells *DTET* that at this point there are no markers—proteomic, genetic, or imaging—that are capable of diagnosing or predicting autism.

"Folks affected by autism are desperate for an early identifier because early treatment makes a difference, but we are just not there yet," Wassink acknowledges. "I don't see the ability to predict autism with a biological test on the horizon, not in the next five years."

Takeaway: Despite hope that there will be a quantifiable means aside from a provider's clinical acumen to detect autism early, there is currently insufficient evidence that genetic, biological, or imaging markers are able to identify those at risk for autism. G2

Research Pushes CTC Characterization to Realize Clinical Value

High hopes abound for the anticipated clinical value of information garnered from circulating tumor cells (CTCs). However, despite plentiful encouraging early reports of ties between the presence of CTCs and clinicopathologic presentations in known cancer patients, more needs to be understood about the basic biology of CTCs and their presumed role in metastasis.

Among the conceivable clinical applications of CTCs include their use as a noninvasive, real-time marker to predict disease progression; as a therapeutic management tool including as an evaluator of therapeutic effectiveness and drug resistance both in clinical practice and as a surrogate end point in clinical trials; as a component of tumor staging criteria; as a means to identify tissue of origin through expression profiling for detection of organ-specific metastatic signatures; and as a screening tool to identify early-stage cancer patients.

"CTC genomics is still in its infancy, mainly due to a lack of technologies capable of isolating sufficient numbers of CTCs to analyze somatic mutations, and the lack of suitable material with which to compare results due to CTC heterogeneity," writes lead author Vicki Plaks, from the University of California, San Francisco, in a perspective piece published in the Sept. 13 issue of *Science*. "The next frontier in the CTC field is their characterization using the constantly improving single-cell "omics" techniques. This will ultimately determine the clinical value of CTCs as biomarkers and therapeutic targets."

Early studies, though, are emerging that demonstrate preliminary signs of the clinical value of. Among the studies linking the presence of CTC to disease progression and survival are the following that were presented at the European Cancer Congress 2013 (Amsterdam; Sept. 27-Oct. 1):

- François-Clément Bidard, M.D., Ph.D., from the Institute Curie in France, led an international effort to contact all European laboratories using CellSearch (Veridex) to gather individual data on metastatic breast cancer patients for pooled analysis. The researchers found that baseline CTC count was significantly associated with

patient performance status, synchronous metastasis, tumor subtype, liver and bone metastases, and carcinoembryonic antigen (CEA) and cancer antigen 15.3 (CA 15–3) levels. Baseline CTC values of greater than 5 CTCs/7.5mL was a significant independent predictor of overall survival. The addition of CEA to the clinicopathological model plus baseline CTC score had a small added effect for overall survival. There was also a significantly added prognostic value of overall survival by incorporating early changes in CTC status at week three to five to the model of clinicopathological factors and baseline CTC scores. This research (which was sponsored by Veridex) the authors say attains a previously unreached statistical power and provides level 1 evidence of the independent prognostic value of CTCs before and during treatment for metastatic breast cancer.

- Researchers led by Sumanta Pal, M.D., from City of Hope in Duarte, Calif., prospectively followed 35 patients with high-risk, localized prostate cancer who had undergone prostatectomy. Based on four sequential 30mL blood draws (two weeks prior and immediately prior to surgery and at four weeks and 12 weeks following surgery), CTCs were detectable in 49 percent of patients prior to surgery (mean cell count, 2.5 cells) and their presence was correlated pathologically to seminal vesicle involvement.

Despite these promising indicators of CTCs pathological significance, challenges remain in understanding the extent to which CTCs are actually predictive of cancer's course and the extent to which CTCs are applicable across a spectrum of cancer subtypes. For instance Plaks points out that variations likely exist in the spatial and temporal distributions of CTCs within the circulation, and that it is plausible that only extremely small and/or plastic CTCs can keep circulating as opposed to those that are possibly filtered by smaller capillaries. This, she argues, could translate into logistical considerations when sampling for CTCs, including the possible need for multiple sampling sites to overcome the filtration and the competing desire to create CTC detection devices that can still identify these very rare cells in small sample volumes to maintain the minimally invasive nature of sample collection. Further, the pathogenic significance of captured CTCs is complicated by the differential gene expression between primary tumors and CTCs, as well as heterogeneity within the CTC population.

NanoString Technologies, BD Biosciences Partner on Development of Single Cell Isolation and Analysis Workflow

NanoString Technologies (Seattle) and BD Biosciences (San Jose, Calif.; a segment of Becton, Dickinson and Company) in early September announced a partnership to develop a single cell isolation and analysis workflow based on the companies' respective nCounter Analysis System and BD FACSJazz Cell Sorting System. The combined workflow solution will enable single-cell gene expression analysis for research applications including in the areas of oncology, immunology, and stem cells.

"Maximizing both the quantity and quality of data that can be extracted from a single cell is critical to the emerging field of single cell biology," said Brad Gray, CEO of NanoString in a statement.

The BD FACSJazz Cell Sorting System is capable of identifying, characterizing, and isolating single or multiple cells—from extremely rare cell populations—and depositing them in 96 and 384 well plates to provide rapid cell isolation, tracking, and identification throughout the process. NanoString's nCounter Analysis System is an automated multiapplication digital detection and counting system that can enable detection of up to 800 genes in a single tube.

"That some CTCs are undetectable and not all detected CTCs have metastatic potential indicates that CTC enumeration is not a good marker for disease staging and prognosis," Plaks writes. "Instead, it is instrumental to design biomarkers based on the gene sets and genomic profile of CTC subsets that predict homing and colonization to specific distant metastatic sites or even sites of primary tumor origin. Advanced CTC analysis is being made possible by constant technical improvements in CTC detection and isolation, although there are still unresolved issues, specifically the need to standardize detection assays."

Takeaway: In order to realize the promise of CTCs much more needs to be understood about their biology and pathogenic role in metastasis. Yet, researchers are encouraged by emerging studies linking the presence of CTCs to clinicopathological presentation in a variety of cancers.

Rapid Testing Shortens Time for Drug Susceptibility Results With TB

Three new rapid tests can significantly cut the time for accurate detection of extremely drug resistant tuberculosis (XDR-TB), according to an abstract presented at the European Respiratory Society's Annual Congress (Barcelona, Spain; Sept. 8-11).

The National Institutes of Health-funded Global Consortium for Drug-Resistant TB Diagnostics studied rapid drug susceptibility tests at clinical sites in India, Moldova, and South Africa with the goal of reducing XDR-TB detection time to a week (compared to the 21 days to three months that traditional methods of drug-susceptibility testing can take) and ascertaining the level of agreement between rapid tests and standard drug susceptibility tests for five drugs with known resistance. The three new tests evaluated were pyrosequencing, a DNA sequencing technique; the HAIN line probe test (Hain Lifescience; Germany), a commercial test that detects genetic mutations in the bacteria; and the microscopic observation drug susceptibility (MODS) test, which screens samples using a microscope.

Based on samples from 1,000 participants, the researchers found that all tests were more rapid than traditional methods with MODS taking 15 days to complete, pyrosequencing taking eight days, and the line probe assay taking five days. All three tests produced highly concordant results to standard testing, ranging from 95 percent to 98 percent for all of the tested drugs. There are trade-offs with the tests, the researchers say. For example MODS is the slowest, but it is also the cheapest of the tests examined.

"Our findings suggest these three tests could provide a quicker way to identify patients who need alternative treatment regimens. This is very important and could potentially save lives as well as help to curb the rise of drug resistant TB," says lead author, Antonino Catanzaro, M.D., from the University California, San Diego in a statement. "It is important to have this range of options available so that TB treatment programs across the world can assess which method is right for them including consideration of the financial restrictions they work within."

Takeaway: Three new tests—pyrosequencing, molecular line probe testing, and MODS—are each accurate and substantially cut the time to results for detecting XDR-TB compared to traditional testing methods. This expanded range of testing options can benefit TB treatment programs across the world.

G2 Insider

Fear Not: Patients Can Handle Online Test Results, Study Finds . . . Concerns by physicians about the repercussions of increasing independent patient access to online laboratory reports may be unfounded. Patients who view their lab test results online overwhelmingly react with positive, rather than negative, emotions, and access to the records does not seem to increase the ordering physician's workload, according to a study published Oct. 3 in the *Journal of Participatory Medicine*.

Kaiser Permanente's online rollout of laboratory test results began in 2005 and was completed in 2007 with the vast majority of test results available to patients at the same time they are available to the ordering physicians. Pathology results, genetic tests, and sometimes HIV results (to comply with state laws) are among the exceptions. Standard ranges for test results, general information about the type of test, any physician comments (such as, "This is heading in the right direction"), and details about follow-up testing are included. Past lab results remain in the members' accounts indefinitely. Kaiser says that viewing of online lab results has steadily increased and is now the most frequently used feature of the online health record with consistently high satisfaction ratings on member surveys.

In this study the researchers conducted an e-mail survey of Kaiser Permanente members, who had viewed at least one test result online within the past year. Based on results from 1,546 respondents (median age 58 years), patients report high levels of satisfaction, appreciation, calm, happiness, and relief. Few experience worry, confusion, fear, upset, or anger from viewing results. The most common follow-up activities after viewing lab test results online were speaking with family or friends about the results, looking up information on Web sites, and making a graph of the pattern of test results over time. Patients whose doctors spoke with them about what to expect from their test results experienced significantly more positive reactions than those who did not speak with their doctors and were also less likely to engage in follow-up activities, including e-mailing and telephoning doctors and scheduling additional appointments.

"The findings that patients largely react positively to seeing test results online should be reassuring," write the authors Kate Christensen, M.D., and Valerie Sue, both from Kaiser. "For practices that have already implemented online test result access but are still limiting access to a small number of results, our findings might provide a good basis for expanding access to results."

Takeaway: Findings that patients largely react positively to seeing test results online should be reassuring to providers since the study confirms that patients want and can handle the results of their laboratory tests.

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