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New Trends, Applications, and IVD Industry Analysis

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FDA Finalizes Guidance for IVD Companion Diagnostics, Announces Upcoming Draft Guidance for LDTs

Several years after the draft guidance was released, the U.S. Food and Drug Administration (FDA) recently finalized its guidance for in vitro diagnostic (IVD) companion diagnostic (CDx) products. Jeffrey Shuren, M.D., director of the FDA's Center for Devices and Radiological Health, called the final guidance "generally consistent" with the 2011 draft but said it provided some clarifications for industry.

The need for guidance, the FDA says, stems from the now "more common" use of therapeutic products for which an accompanying test "is essential" for the therapy to meet its labeled safety and effectiveness claims—namely the identification of subpopulations of patients for whom the treatment will be effective or pose increased risk of serious, adverse events. Additionally, an IVD CDX would be deemed essential if treatment is adjusted based on response monitoring to achieve improved safety or effectiveness.

"Inadequate performance of an IVD CDx could have severe therapeutic consequences," the FDA warns in the final guidance. Thus, a risk-based approach will be used to determine whether premarket approval or 510(k) clearance is needed for the IVD CDx.

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Opportunity Still Exists for Companion Diagnostic Partnerships

Companion diagnostics (CDx) hold the promise to make drug therapies safer and more effective. At the same time, breaking the conventional trial-and-error cycle for prescription medications makes health care more cost-efficient by allowing health care providers to give the right drug to the right patient.

Pharmaceutical companies increasingly understand that incorporating a CDx strategy into drug development programs at early stages may expedite trials and, ultimately, the drug approval process. Utilization of CDx at a time when the health care market is increasingly focused on achieving improved outcomes and cost efficiencies in turn further drives continued interest in CDx test development. To date, CDx development has been achieved largely through partnerships between pharmaceutical and diagnostics companies. Big name

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The FDA clarified that "in most circumstances an IVD CDx and its corresponding therapeutic product should be approved or cleared contemporaneously by the FDA." Planning for this, the FDA hopes, will occur "at the earliest stages of development." Cases in which contemporaneous development may not be possible include a novel IVD device for a new analyte, a new version of the device by a different manufacturer, or an existing device cleared or approved for another use.

Regulation of LDTs Coming

In addition to finalizing guidance for IVD CDx, the FDA simultaneously announced its congressional notification and draft framework on the regulation of laboratory-developed tests (LDTs), including LDTs for CDx. The agency must legally give Congress 60 days' notice and a summary of any impending guidance for regulation impacting LDTs.

"To the extent that stakeholders have concerns about possible regulatory gaps under CLIA, ACLA has long supported enhancing the CLIA regulatory framework, rather than impose an additional layer of regulation based upon a different statute designed for manufactured products rather than laboratory testing."
—Alan Mertz, ACLA

The coordinated announcements ignited immediate reactions and exposed a sharp divide in the testing industry between the interests of IVD makers and laboratories running LDTs. The lab industry has long questioned the FDA's authority to regulate LDTs, which it calls a service, not a device, while the IVD interest supports FDA regulation of LDTs, which they say will level the playing field.

"AdvaMedDx welcomes the publication of the draft framework on a risk-based approach to the regulation of LDTs," said Andrew Fish, executive director of AdvaMedDx, which represents IVD manufacturers. "These types of tests are increasingly being used to diagnose and guide the treatment of potentially life-threatening conditions, and FDA oversight of higher-risk diagnostic tests including CDx, regardless of the manufacturer, is essential to patient safety. . . . AdvaMedDx's membership supports a modernized and flexible approach to the review process for diagnostics."

In contrast, the American Clinical Laboratory Association (ACLA) urged the FDA to "exercise caution," expressing concern that additional regulation could stifle diagnostic innovation and ultimately jeopardize patient access. ACLA supports any additional regulation of LDTs to come through expansion of the CLIA framework.

"The massive leaps in scientific and medical advancement that have occurred over the last quarter century have yielded a bounty of new tests created by highly trained physicians and clinicians that were not even imagined when CLIA was last updated in 1988," said Alan Mertz, president of ACLA, in a statement. "To the extent that stakeholders have concerns about possible regulatory gaps under CLIA, ACLA has long supported enhancing the CLIA regulatory framework, rather than impose an additional layer of regulation based upon a different statute designed for manufactured products rather than laboratory testing."

Takeaway: Despite lab industry concerns over regulation of LDTs, the FDA is moving forward with oversight plans. G2

▲ **Opportunity Still Exists for Companion Diagnostic Partnerships,** *from page 1*

diagnostic companies such as Abbott Molecular, Qiagen, and Foundation Medicine are deeply invested in these partnerships.

Currently, 155 pharmacogenomic biomarkers are included in Food and Drug Administration-approved drug labels. The pharmaceutical industry is invested in a more customized drug development model. The Personalized Medicine Coalition estimates that 30 percent of all treatments in late clinical development rely on biomarker data, as do 50 percent of all treatments in early clinical development and 60 percent of all treatments in preclinical development.

"If we could look back to the first CDx case, HER2/Herceptin, and if we could get the true story, I'm sure there were bumps and bruises along the way," Harry Glorikian, a health care consultant, tells *DTET*. "Although there are still problems, as science doesn't always progress as expected, these partnerships now go a lot smoother. We know how to handle problem 'A' or avoid it altogether. Mistakes of the past won't be made again."

The financial arrangements and interworkings of these collaborations are often not disclosed, and while there is no objective measure of the success of these ventures, experts predict these joint ventures will continue and result in a heightened number of commercial launches of codeveloped drugs and CDx tests over the next 10 years.

"If there are three drugs that basically do the same thing, you can select on best price, but nobody wants to play the price game. So, if I give you a tool to achieve a better outcome by targeting the ideal population better or improving adherence, you may decide to use my drug."
—Harry Glorikian, health care consultant

"If the United States is driving towards outcomes-based system and institutions are reimbursed based on outcomes, they are going to demand products that help them achieve those better outcomes," Glorikian explains. "If there are three drugs that basically do the same thing, you can select on best price, but nobody wants to play the price game. So, if I give you a tool to achieve a better outcome by targeting the ideal population better or improving adherence, you may decide to use my drug."

Sampling of Recent CDx Partnerships

The sampling of CDx partnerships announced this summer demonstrates the breadth of partnerships—varying in stage of compound development and the range of medical conditions involved (oncology, infectious disease, reproductive health):

- **Ventana Medical Systems** (a Roche company; Tucson, Ariz.) announced in July a new partnership with Merck for the development and commercialization of a CDx for an undisclosed oncology target. Ventana reports working with more than 45 biopharmaceutical partners on more than 180 collaborative projects to develop and commercialize CDx globally.
- AstraZeneca said the circulating DNA (ctDNA) test it is codeveloping with **Roche** (Switzerland) will be designed to identify epidermal growth factor receptor (EGFR) mutations in both tumor tissue and plasma from patients with non-small-cell lung cancer (NSCLC). The test will optimize the clinical development of investigational compound AZD9291 for patients who are resistant to first-generation EGFR tyrosine kinase inhibitors (TKIs).

- With longtime partner **Qiagen** (Germany), AstraZeneca will codevelop a test to identify patients that can be treated with Iressa, an EGFR-TKI. Iressa, already approved in 65 countries, is indicated for the treatment of adults with locally advanced or metastatic NSCLC with activating mutations of EGFR-TK. The test uses a highly sensitive assay to detect EGFR mutations in small fragments of plasma ctDNA. AstraZeneca and Qiagen said the test has demonstrated "robust and reliable" identification of EGFR mutation status using samples from the Phase IV IRESSA Follow Up Measure study.
- **Biocartis** (Belgium) and **Abbott** (Abbott Park, Ill.) will leverage Biocartis's molecular diagnostics system, Idylla, and Abbott's regulatory, scientific, and commercialization expertise to develop multiplex biomarker panels for use in partnership with pharmaceutical companies' clinical trials.
- Ferring Pharmaceuticals and Roche announced a collaboration to combine diagnostic testing technology from Roche with Ferring's human cell line-derived recombinant follicle-stimulating hormone, currently in phase III development. This combination will personalize infertility treatment dosing based on a woman's anti-Müllerian hormone levels.
- **Cepheid** (Sunnyvale, Calif.) announced earlier this summer a new collaboration with AstraZeneca, Cubist Pharmaceuticals Inc., and GSK to promote "transformational change" in infectious disease therapy with the development of a rapid diagnostic test that can target multi-drug-resistant pathogens and aid the appropriate use of antibiotics. The group will work to extend the number of body sample types utilized by the Xpert Carba-R rapid test. Xpert Carba-R is commercially available outside the United States and is targeted for a commercial U.S. release in 2015, subject to approval.
- **Foundation Medicine** (Cambridge, Mass.), in June joined pharmaceutical companies Amgen, Genentech, Pfizer, and AstraZeneca in the Lung Cancer Master Protocol (Lung-MAP) trial. Lung-MAP is a multidrug, multiarm, biomarker-driven clinical trial for patients with advanced squamous cell lung cancer. Foundation Medicine's comprehensive genomic profiling will be used to match patients to one of five experimental drugs—four targeted therapies and an anti-PD-L1 immunotherapy—based on the tumor's genomic profile.

Takeaway: Codevelopment of CDx through diagnostic-pharmaceutical partnerships will continue to permeate the industries. These collaborations will culminate in accelerated commercial availability of targeted therapeutic products that will assist the health care system to achieve improved outcomes at a reduced overall cost.

Smaller Companies Can Participate Too

While headlines trumpet the major partnership players—Abbott, Roche, Qiagen, and Foundation Medicine—some startups have been able to establish collaborations with pharmaceutical companies. Smaller companies' lack of a footprint may make them less ideal partners.

"If I'm a pharmaceutical company and I am going to launch a drug globally, I need a partner that can go global with the product," explains Glorikian. "There may be kinks if the [smaller company] doesn't have marketing, distribution, and commercialization in place."

Startups like Nodality (San Francisco) have positioned themselves in active pharmaceutical partnerships, although to date no commercial products have been produced. Nodality's proprietary platform, Single Cell Network Profiling, which enables functional characterization of disease-associated signaling, is being applied to develop molecular diagnostics in cancer and autoimmune diseases.

Nodality is also collaborating with pharmaceutical partners on patient stratification and companion diagnostics development and biomarker discovery and development. Existing partnerships include CB Pharma, Pfizer, and Janssen Biotech.

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Inside the Diagnostics Industry

NextCODE Tackles Genome Interpretation Bottleneck

Jeff Gulcher, M.D., Ph.D., co-founder, chief scientific officer, NextCODE

NextCODE Health (Boston) has launched clinical genomic services leveraging a platform originally developed at deCODE genetics. With the advent of affordable whole-genome sequencing, NextCODE's end-to-end solution is designed to tackle the interpretation and data management bottleneck to expedite the incorporation of sequence data into clinical care.

NextCODE secured a five-year, exclusive license for the genomics platform—including the information technology (IT) infrastructure and data analysis capabilities—from Amgen, which acquired deCODE genetics in December 2012. NextCODE also secured $15 million in Series A financing in fall 2013. This is enabling NextCODE to rapidly scale the integration of its genomics services into clinical settings. NextCODE's services include clinical- and research-grade sequencing, analysis of clients' legacy data, genome interpretation tools, and big genomic data solutions proven scalable for the efficient management of genomic and medical data on up to hundreds of thousands of patients.

Analysis and interpretation by the Clinical Sequencing Analyzer (CSA) are powered by the proprietary Genomic Ordered Relations (GOR) database. The CSA is also backed by what the company says is the world's largest clinical genomics reference database, including more than 40 million validated variants paired with clinical data. Together the GOR and CSA enable real-time confirmation of potentially pathogenic mutations through visualization of raw sequence reads, while the Sequence Miner tool enables researchers to perform sophisticated real-time queries and data mining on tens thousands of samples.

DTET recently spoke with Jeff Gulcher, M.D., Ph.D., co-founder and former chief scientific officer of deCODE and now co-founder and chief scientific officer of NextCODE, to learn more about the company's platform and genomic services as well as industrywide challenges to the adoption of clinical next-generation sequencing testing.

The scale of data the NextCODE system can handle is remarkable. Can you tell us about the system's development.

We came from deCODE where we developed software for systems to deal with both the research and clinical aspects of large amounts of genetic data. Our goal was to enroll most of the Icelandic population, a little more than 300,000 people, and we successfully enrolled well over half of the adult population with blood samples and informed consent to use medical data. Over the years we built up this very large biobank in Iceland and then had another 300,000 from outside Iceland for confirmation studies. When we started out, we were using microsatellite markers. So we were measuring 2,000 markers per patient times 150,000 patients, and we had no trouble using a conventional database infrastructure. These are traditional databases designed for bank transactions, and the average person isn't going to do more than 2,000 to 3,000 bank transactions per year.

But when we got into the DNA chip era, we started measuring 1 million single nucleotide polymorphism markers per patient. And what we found was that when we tried to load in 1 million columns (each marker needs its own column) times 150,000 patients, we had enormous problems. The problem was not in storing the data, but in getting the data out. You had a huge input-output problem, and when you tried to hunt for a subset of those millions of markers in a subset of

those 150,000 patients, the system just gummed up. It just couldn't get the data out quickly enough for statistical algorithms to handle or for immediate quality control.

That is when we invented a different way of storing this huge amount of data. We call it the GOR—Genomically Ordered Relational—database infrastructure. The principle is very simple: to make sure all of the data you have are tied to genomic positions. With DNA data, chip data, RNA data, or annotation data it is easy to ascribe it a specific location in the whole human genome. As a result, your algorithms end up being orders of magnitude more efficient than if you were to use a traditional relational database. That's what we initially designed eight or nine years ago, and it continues to work very well for us now in the sequencing era. Today you don't have 1 million but 3 billion letters you need to keep track of per genome, so we've solved a problem that everyone who is going to sequence whole genomes is about to face.

What is the business case for using NextCODE's services?

With sequencing, a big data problem ends up being an enormous data problem. You see academic groups trying to retrofit Oracle and IBM databases to handle this much data and it ends up crashing. They just aren't able to access their own data.

The broad business case for using NextCODE's platform is that it offers a holistic solution to many of the shortcomings that clinical geneticists currently face using traditional technology. Even in major medical centers with substantial expertise in genetics, clinicians are often analyzing data by running bespoke R and Perl scripts that have to be generated by their bioinformaticians. And the results come back as Excel tables with lists of potential causative variants that they then have to follow up on one-by-one.

"With sequencing, a big data problem ends up being an enormous data problem."
—Jeff Gulcher, M.D., Ph.D.

By making it possible to correlate all the variants in the genome with all the public and proprietary annotation data available, in real time, our system delivers huge time savings as well as increased power to find causative variants. That translates into better care, and our customers have reported many instances of our tools solving cases in which other approaches had failed. With current approaches, many leading medical institutions report that they can solve about 25 percent of pediatric rare disease cases. The feedback we are getting from our users suggests NextCODE tools can increase that yield substantially. For the medical system, that means huge savings in terms of ending diagnostic odysseys earlier and making it possible to get through more cases in a much shorter time. The business case in that sense is compelling on several fronts.

We talk to lots of academic centers that may be sequencing 100 genomes per month on the clinical side and hundreds on the research side. They would like solutions to aggregate the data and learn something more than just making a diagnosis in an individual, although in most cases they won't be able to make a diagnosis because most patients don't have a disease mutation that's already known. The information can be quite useful to collate, yet in order to do that you must be able to store data efficiently and have algorithms to query it swiftly to discover new things.

That's the other part of our business: to enable groups to aggregate data rather than just sequence a patient and make a diagnosis and never use the data again. That is

throwing away valuable information and we can provide a mechanism and set of tools and infrastructure that enables them to use it. We are also working with big pharma companies in order to make use of big next-generation data sets. We see them as natural customers for this system. They need these tools to be successful. And there are other population-scale projects like Genomic England, which is going to sequence 100,000 people in the United Kingdom in the context of clinical care. It is a very large project, and we hope to take part in it and several other large projects around the world that are following in the footsteps of deCODE's work in Iceland.

Your clients to date are primarily clinicians at large, academic centers. Do you have plans to sell services to smaller laboratories?

Yes. Our customer base includes diagnostic laboratories that do not have extensive informatics expertise. One of the advantages of our system is that it enables smaller labs to begin offering whole-exome and whole-genome testing without having to build up their own IT infrastructure.

One of the notable features of your service is its user-friendly interface. How can this aid clinicians less comfortable with interpreting genomic test results?

When you talk to even some top medical centers, they are taking sequence data and the informatics department is doing by hand what our tools can provide systematically and efficiently. What do they provide to the physician? Not a nice system to ask questions of the data. Instead they give the geneticist an Excel table with hundreds of variants and he or she must now sort to make a diagnosis. I still can't believe it when I see this.

We made interfaces that let clinicians analyze their patients' genomes and all of the annotation data available, using signs and symptoms as simple search terms. By clicking on different buttons they can integrate different inheritance models, commonly used or custom-made panels of genes, and filter out all common variants to quickly narrow their search to rarer or even novel variants. So a clinical geneticist can search the entire genome, hone in quickly on the culprit variant, and instantly visualize it in all the raw sequence reads for confirmation. They can trust their own eyes rather than a black-box algorithm. They can drill down to look at the function of the variant—what effect it has on protein structure—to end up with a detailed picture of the root of the patient's disease. All of this is summarized in concise and comprehensible terms, so that it can inform a diagnosis and treatment options.

How can these results be integrated into electronic health records (EHRs)?

In order to bring genomic data into clinical care, the results of genomic analyses have to be simply and seamlessly integrated into patients' medical records. For this reason we have made all our systems HL-7 compatible, and this compatibility is critical in two ways. First, the CSA is able to extract information from medical records and lab results to provide the phenotypic information that needs to be correlated with sequence data to inform the analysis and diagnosis. Once the analysis is complete, the CSA then stores the detailed data used and distils it into a concise form that can be uploaded to an EHR.

NextCODE By-the-Numbers

$1 billion invested in development of platform with capabilities including:

- Proven scalability to 350,000 whole genomes
- 40 million-plus validated variant frequencies generated from mining 30 times more data than the 1000 Genomes Project
- 10 times decrease in hands-on-time for genetic diagnosis
- Analysis and IT behind 350-plus publications

Genetic Counselors See Job Evolving: Further Changes Expected With Growth of Clinical Sequencing

While the majority of genetic counselors (GCs) report working in a direct clinical role, a growing number work in nonclinical capacities, primarily in laboratories. According to the National Society of Genetic Counselors 2014 Professional Status Survey, 16.6 percent of GCs work in a diagnostic laboratory (either commercial or academic), compared to 10.9 percent in 2010.

"As the number and complexity of tests increase, more and more clinical decisions are dependent on the laboratory," says Theresa Boomer, a clinical laboratory liaison at Sequenom Laboratories (San Diego). "While decisionmakers will always be in the clinic, they also need to be in the laboratory. General physicians have never really been educated [about molecular genetics], beyond straightforward tests."

GCs are in a unique position to bridge the clinical and laboratory environments, brining benefit to both. Utilization of GCs improves patient care with effective counseling and enhanced results interpretation, while optimizing health care spending through ensuring appropriate test ordering.

"You can only fake it for so long—trying to do genetic counseling with other resources on board that are already paid for," said Boomer. "But you get a heck of a lot of bang for the buck with a GC."

The "intangible value" that clinical geneticists provide has partially been responsible for the delay of laboratories in incorporating GCs as part of the molecular team, explains Boomer, who spoke at G2's MDx*NEXT* conference (Baltimore; June 11-13) on what laboratories need to know about genetic counseling.

"You can only fake it for so long—trying to do genetic counseling with other resources on board that are already paid for."
—Theresa Boomer, board-certified genetic counselor

"I have heard it said that GCs don't make you money, but will save you money," Boomer tells *DTET*. "But part of the benefit that a GC brings to a test is intangible. It is not black and white. Ninety-five percent of the value of a test is in accurate interpretation. GCs have the ability to put the whole testing process in context, and the value is in that end point. The value added by GCs may drive orders from Lab A to Lab B. The support may differentiate laboratories, and it is essential if you are paying $3,000 for a test."

GCs Improve Test Ordering

Utilization of a genetic health care provider during the BRCA test ordering process improves the appropriateness of the test type ordered and significantly increases adherence to nationally recommended genetic counseling practices, according to a study published in *Genetics in Medicine* on June 12.

A total of 473 enrollees in the Inherited Cancer Registry for whom BRCA testing had already been completed were surveyed to evaluate patients' recall of pretest genetic counseling for hereditary breast and ovarian cancer. Additionally, BRCA test reports were assessed to determine appropriateness of the BRCA test type ordered and to determine type of ordering test provider (a master's degree-trained GC, board-certified medical geneticist, or nongenetic provider).

Among the cases in which a genetic health care provider placed the test order (58 percent of all cases), 97 percent of patients recalled a pretest discussion. In contrast, of the 42 percent of tests ordered without a genetic health care provider (i.e., obstetrician, gynecologist, oncologist, nurse practitioner) involved, only 59 percent of participants recalled a pretest discussion. Among the 385 total participants who recalled a pretest discussion, those with involvement of a genetic health care provider had higher adherence to eight recognized genetic counseling elements, four of which were statistically significant (family history assessment, discussing anti-discrimination laws, insurance impact, and being provided a session summary). Years since testing, personal cancer history, and BRCA status did not impact these results. In 266 patients, single-site testing (for a known familial BRCA gene mutation) or multisite-3 testing (for three BRCA mutations highly prevalent in Ashkenazi Jewish cases) would have been sufficient. Involvement of a genetic health care provider in these cases cut the chances that a comprehensive test was ordered by half.

Nationally Recommended Elements of Pretest Counseling

- Family medical history
- Potential hereditary cancer syndromes
- Potential health care management impact
- Potential lack of conclusive test results
- Implications for other family members
- Impact of test results on insurance
- Take home educational tools or session summary

Source: Adapted from Cragun D, Camperlengo L, Robinson L, et al. "Differences in BRCA counseling and testing practices based on ordering provider type." Genetics in Medicine. *Published online 12 June 2014.*

Unnecessary ordering of the comprehensive test is costly. The authors say that there is roughly a tenfold price difference between the comprehensive panel and the two more limited BRCA testing options (roughly $3,000 versus less than $400 per test). Recognizing the key role that GCs can play in improving appropriate test ordering, Cigna became the first national insurer to implement a policy whereby counseling by a certified genetics professional (either a board-certified genetic counselor or medical geneticist) is required prior to testing for BRCA, as well as testing for hereditary colorectal cancer and Long QT syndrome. It has been reported that this policy was implemented in response to the finding that 20 percent of these hereditary cancer tests are ordered inappropriately.

In the BRCA study, the authors, led by Deborah Cragun, Ph.D., from the H. Lee Moffitt Cancer Center in Tampa, Fla., write that, "Our findings suggest that there may be potential cost-of-care implications associated with genetic health care provider involvement."

NGS Further Impacts Counseling

While the argument has been made that the declining cost of whole-genome sequencing (WGS) and whole-exome sequencing (WES) make it more cost-effective than single-mutation or small-panel analysis of genes, the comprehensive testing fails to incorporate the extended interpretation necessary for reporting of results back. Sequencing's impact on the process of genetic counseling can already be seen.

Although relevant, actionable incidental findings from WES appear from limited clinical experience to be rare, pretest and posttest genetic counseling are required as a small number of well-described disease-association mutations could have clinical consequences. Given that counseling a patient regarding every possible finding is not feasible, genetic counselors are shifting the context of pretest and consent discussions toward the big picture, rather than very disease-specific conversations.

"The return of results discussion for WES is really about broad ideas about adult-onset and treatable conditions, Laura Amendola, a genetic counselor at the Univer-

sity of Washington Medical Center in Seattle, tells *DTET*. "There is not enough time to discuss every single condition, and really patients don't have enough bandwidth to process that amount of information."

Amendola says that in her experience, primarily with WES testing of middle-aged research subjects, there have not been a lot of high-risk genetic conditions identified, but rather incidental findings are related to pharmacogenomic genes, which overall, patients are happy to learn about.

"In returning results, patients expect more," says Amendola. "We have to prepare them for what we actually get out of whole-exome and whole-genome testing. We have to manage expectations about what we do and do not know."

As genetic counselors reframe the counseling context in light of clinical application of WGS and WES, they are also involved in research to elucidate patient preferences for the return of incidental findings. Prelimary data, based on the first 200 families referred to Ambry Genetics (Aliso Viejo, Calif.) for diagnostic exome sequencing, suggest that families overwhelmingly opt to receive information on incidental or secondary findings. Although, it appears that current health status may influence patient decisions for disclosure of incidental findings, according to the study published online in October 2013 in *Genetics in Medicine*.

While many participants in research studies want to receive secondary findings, these individuals are likely healthier or facing non–life-threatening disease, compared with those patients undergoing diagnostic exome sequencing who "represent an extreme end of the health spectrum," the authors note.

Ambry requires genetic counseling and consent in order for patients to accept or decline secondary findings disclosure. Ambry's reportable secondary findings include "only medically reviewed and previously defined mutations in characterized genes." During consent, secondary findings are characterized as carrier status of recessive disorders, predisposition to later-onset disease, predisposition to increased cancer risk, and early-onset disease (the only secondary findings category available for children). One the consent form adult patients can choose whether to receive secondary findings for the four categories.

Among the first 200 diagnostic exome sequencing patients, the majority (93.5 percent) chose to receive secondary results in one or more categories. Of the patients tested, 162 were children (affected with complex diseases including severe cognitive impairment and a truncated life expectancy) and had an average age of 5 years. Minors were only eli-

Reporting, Counseling Strategies Undertaken by eMERGE

The electronic Medical Records and Genomics (eMERGE) network was established in 2007 to further genomic discovery by using biorepositories linked to the electronic health records (EHRs). According to a review published March 26 in *Frontiers in Genetics*, individual sites within the eMERGE network are exploring acceptable mechanisms, including reliance on genetic counseling, to address incidental findings.

- Northwestern University (Illinois) is returning potentially actionable findings (Factor V Leiden mutation and the hereditary hemochromatosis HFE mutations) by reconsenting 150 biobank participants who were genotyped during Phase I of eMERGE. Results will both be deposited in the EHR for physicians and sent (mail or online) to study participants. Participants can discuss the results during an appointment with the physician or be referred to a study genetic counselor.
- At the University of Washington-Group Health site (Seattle), 450 participants will be genotyped for pathogenic variants in six highly penetrant pharmacogenes (for malignant hyperthermia, long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and LDLR for hyperlipidemia). The Department of Clinical Genetics will return results with appropriate counseling and subsequent EHR documentation.
- Geisinger Health System (Danville, Pa.) investigators are developing a laboratory report that summarizes results of WGS in individuals with intellectual disability and normal chromosomal microarray to identify an underlying genetic etiology. Causal variants and incidental findings (from the ACMG list) will be validated and all patients will be informed about the results and undergo counseling.

gible for reporting of early-onset secondary findings, and only seven guardians did not consent to this reporting. Adults tested (n = 38) had an average age of 38 years and milder disease manifestations than the children. Six of the 38 adults did not consent to reporting of at least one category. Among responses for blinding, preferences were evenly distributed among categories, which the authors say reflects "an intricate and complicated" decisionmaking process likely based on personal life experiences.

"Individuals pursuing diagnostic exome sequencing may be more active in seeking medical information and therefore more receptive to obtaining secondary findings information than healthy individuals," write the authors, led by Layla Shahmirzadi, from Ambry.

GCs Work to Improve Lab Reports

In addition to evaluating mechanisms of consenting patients and directly reporting results to them, genetic counselors are involved in research to optimize laboratory reports to return sequencing-based test results to ordering physicians, who may have limited genomics understanding.

"Our process for the development of WES clinical reports has shown that accurate and open communication between the clinician and laboratory is ideally an ongoing process, both for individual reports and for general report formatting," says Michael Dorschner, Ph.D., from the University of Washington in a paper published in the March issue of *American Journal of Medical Genetics*.

As part of a research protocol, the researchers compared panels (25 genes) to sequencing for the clinical evaluation of genetic susceptibility to colorectal cancer/polyposis (CRCP). Exome sequencing evaluated the same 25 CRCP-related genes plus 96 non-CRCP genes that may contain actionable incidental findings and nine pharmacogenetic genes. Using an iterative process with feedback from clinical geneticists, genetic counselors, nongeneticist physicians, genomicists, bioethicists, molecular laboratory experts, and a research coordinator, the group ultimately developed a standard test report modeled after those used for targeted gene panels.

"Non-geneticists, who are less comfortable communicating results of genetic testing, unanimously asked for clarity," Dorschner reports. "Getting to the punch line early in the report and providing more guidance with respect to recommendations were among their requests. . . . Many clinicians are ill equipped to understand the limitations of complex WES/WGS testing and it is incumbent on the laboratory to provide guidance with respect to the completeness of testing."

Takeaway: As more data is gleaned on patient preferences, and professional organizations establish uniform standards for reporting of findings of whole-exome and whole-genome examinations, genetic counselors are positioned to play a key role in informing this ongoing discussion and in implementing effective strategies during this transition period.

Exome Sequencing-Based Lab Reports

The most desired features identified by University of Washington researchers in optimizing comprehensive reports of WES data include:

- Two separate reports, one for indication-specific genes and one with incidental findings.
- Results and interpretation sections were placed at the beginning of the report, and the test methods were moved to the end.
- A mix of basic and higher-level information was needed to satisfy clinicians less comfortable with genetic testing and nongeneticist physicians with an interest or experience in genetics.
- Standard test report elements were supplemented with research study-specific language, which highlighted the limitations of exome sequencing and provided detailed, structured results and interpretations.

Preemptive Pharmacogenomic Testing Can Be Successfully Implemented, Integrated Into Care

Pharmacogenomic (PGx) testing is at the epicenter of personalized medicine, with the promise that accessible genomic information will lead to more informed prescribing practices—enabling prescription of the proper drug at the correct dose, the first try.

A special issue of the *American Journal of Medical Genetics* (*AJMG*) Part C (Seminars in Medical Genetics) was recently dedicated to implementation of genomic medicine. *DTET* reviewed two of the special issue's published case reports detailing development of preemptive PGx programs, the implementation of testing and reporting of identified variants, and the acceptance of the program by clinicians. The lessons learned by the University of Chicago (UC; Illinois) and St. Jude Children's Research Hospital (Memphis, Tenn.) can provide valuable insight to other laboratories and institutions contemplating establishing such programs. In both of these cases, PGx decision support was successfully implemented due to the availability of data reported from high-quality genotyping arrays.

University of Chicago

The 1,200 Patients Project at UC was considered successful because "patient interest was robust, physician adoption of information was high, and results were routinely utilized," reports Peter H. O'Donnell, M.D., principal investigator of the project in *AJMG*.

The 1,200 Patients Project offers free, broad, preemptive PGx testing to outpatients seen at UC. Enrollment is continuing at a pace of roughly 30 patients per month. Patients are eligible if, at enrollment, they are regularly using one to six prescription medications. Genotyping was performed using a MASS-ARRAY/matrix-assisted laser desorption/ionization time-of-flight mass spectrometry method (Sequenom) at Knight Diagnostic Laboratories (Oregon Health & Science University). Both a custom-designed and commercially available PGx panel (Sequenom) were used.

"Establishment of a validated, custom-designed genotyping panel to generate accurate genotype calls in a CLIA environment was not trivial." —Peter H. O'Donnell, M.D.

"Establishment of a validated, custom-designed genotyping panel to generate accurate genotype calls in a CLIA environment was not trivial," O'Donnell explained. "Validation required repeat testing of reference samples, analysis, and refinement of the panel over a span of approximately six months, and some genotype calls for validated assays nevertheless remain inconsistently reportable, although the overall frequency of missing calls is low." O'Donnell cited CYP2D6 genotypes as particularly plagued with "technical hurdles" and they were not initially reported.

PGx results are made available to enrolled physician-patient pairs through the Genomic Prescribing System (GPS) portal, which also provides real-time prescription guidance. Results were delivered in the form of "traffic light" signals, with green (favorable), yellow (caution), and red (high-risk). Each signal had a corresponding "clinical summary" that was viewable with a mouse click and provided a clinical translation of the PGx result, designed to be read in 30 seconds or less. Clinic providers were given daily reminders of which patients with scheduled appointments were enrolled and had been genotyped.

In *AJMG*, the UC researchers reported 812 patients had participated (90 percent of those approached) along with six physicians (all remained enrolled). Of the 608 patients who had been successfully genotyped, there were 268 clinic encounters at which results were accessible via the GPS. At 86 percent of these encounters, physicians accessed the GPS,

receiving 367 result signals for medications patients were currently taking (57 percent green, 41 percent yellow, and 1.4 percent red). Clinical summary click frequencies varied by alert severity, with 100 percent of red clicked, 72 percent of yellow, and 20 percent of green.

Workflow analysis suggests, the authors say, that drug comparison information is being "under-utilized so far during new prescription decisions by our early-adopter physicians." The authors say GPS is being checked ahead of the visit, rather than while in the room with the patient. For the vast majority of visits (85 percent), clinical PGx information was available for at least one drug the patient was taking, "suggesting relevance of the delivered information," the authors write. "The lifetime impact on drug prescribing is potentially immense: ≈25 percent of [tested] patients have a genotype which would confer a red light signal for at least one of the drugs for which we report results, and over 50 percent of patients would have a level yellow light alert for at least one drug with results in our system."

The authors do acknowledge that the value of preemptive testing will ultimately be determined through the evaluation of outcomes measures. In the future, "other high-throughput genotyping options" will be evaluated in order to expand the service, control marginal costs, and cut turnaround times.

St. Jude Children's Research Hospital

Researchers from St. Jude similarly report that preemptive clinical pharmacogenetics has proven "feasible, clinically useful, and scalable." The institution's translational research experience, which initially focused on implementation of pharmacogenetics as standard of care for its patients, with single-gene tests (TPMT and CYP2D6), was "substantially" expanded in 2011 through the introduction of the PG4KDS research protocol, which called for preemptively genotyping patients for multiple genes.

"It is important to highlight that a clinical research approach is not essential for implementation of a hospital-wide pre-emptive PGx program."
—James Hoffman, Pharm.D.

"We elected to implement array-based clinical PGx in the context of a clinical trial," write the authors, led by James Hoffman, Pharm.D., the medication outcomes and safety officer at St. Jude. "It is important to highlight that a clinical research approach is not essential for implementation of a hospital-wide pre-emptive PGx program. Other large scale implementations of pre-emptive PGx have been successful in the context of routine clinical care."

The Pharmacogenetic Oversight Committee provides oversight for the PG4KDS study and determines which gene test results should be placed in the EHR, what constitutes priority (high-risk) diplotypes, which drugs should be linked to genetic test results, and preferred methods of notification.

In *AJMG*, the St. Jude researchers report that genotyping occurred for 230 genes, including 1,936 loci relevant to pharmacogenomics. Testing was performed by the Medical College of Wisconsin in a CLIA-certified laboratory using Affymetrix's Drug Metabolizing Enzymes and Transporters Plus array, supplemented with a CYP2D6 copy number analysis using a quantitative polymerase chain reaction test. Test results for four genes (TPMT, CYP2D6, SLCO1B1, and CYP2C19) coupled to 12 high-risk drugs have been incorporated into electronic health records (EHRs) for clinical implementation with 55 clinical decision support rules. EHR results are tied to an interpretive consult and interruptive alerts at the time of prescription or dispensing.

"Our prioritization of new gene/drug pair implementation has relied heavily on the availability of Clinical Pharmacogenetics Implementation Consortium (CPIC) guide-

lines," write the authors. "Gene/drug pairs are prioritized for migration to the EHR based on a variety of criteria: inclusion in guidelines by CPIC or other professional organizations, [Food and Drug Administration] labeling recommendations, evidence of reimbursement for genetic testing for that drug's use, the availability of a stand-alone CLIA-approved test for the individual gene, and the publication of clinical trials linking drug effects to functional pharmacogenetic loci."

Through August 2013, the researchers report in *AJMG* that 1,559 patients have been enrolled, with genotype test results available for 1,016 patients. More than three-quarters (78 percent) had at least one high-risk (i.e., actionable) genotype result placed in their EHR. Average turnaround time has ranged from 20 days to 137 days, which the authors say is OK given the research protocol and with testing done for preemptive purposes, although they estimate that it could be optimized to a "practical" time of 14 days to 21 days.

"Key elements necessary for our successful implementation have included strong institutional support, a knowledgeable clinical laboratory, a process to manage any incidental findings, a strategy to educate clinicians and patients, a process to return results, and extensive use of informatics, especially clinical decision support," the authors conclude. "We plan to implement at least eight new gene test results into the EHR over the next three years (e.g., DPYD, UGT1A1, G6PD), along with additional drugs, based partly on the output from CPIC over the next several years."

Takeaway: Preemptive PGx genotyping programs have been successfully implemented. A key element of success is the incorporation of PGx-related clinical decision support in the EHRs to ensure the results can inform clinical decisionmaking.

2014 CPIC PGx Dosing Guidelines

The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Pharmacogenomics Knowledge Base have combined genomic and clinical information to establish clinical practice guidelines enabling clinicians to understand how to use PGx test results to optimize drug therapy. The group says that a key assumption behind their guidelines is that clinical high-throughput and preemptive genotyping will become more widespread.

The following dosing guidelines have been issued or updated by CPIC in 2014.

Drug	Variant	Recommendation
Abacavir	HLA-B	For HLA-B*57:01-+, abacavir is not recommended
PEG-interferon-alpha-containing regimens	IFNL3	Patients with the favorable response genotype (rs12979860 CC) have increased likelihood of response (higher sustained virologic response rate) to hepatitis C virus treatments with PEG-IFN alpha
Fluoropyrimidines	DPYD	Alternative drug for patients who are homozygous for DPYD nonfunctional variants; 50 percent reduction in starting dose for heterozygous patients (intermediate activity).
Codeine	CYP2D6	Alternate analgesics are recommended for CYP2D6 ultrarapid and poor metabolizers
Ivacaftor	CFTR	Treatment only recommended in cystic fibrosis patients who are either homozygous or heterozygous
Rasburicase	G6PD	Contraindicated in G6PD deficient patients
Simvastatin	SLCO1B1	In patients with the C allele at SLCO1B1 rs4149056, there are modest increases in myopathy risk even at half doses (40 mg)

G2 Index Up 9% in 2014, Surpassing Broader Market

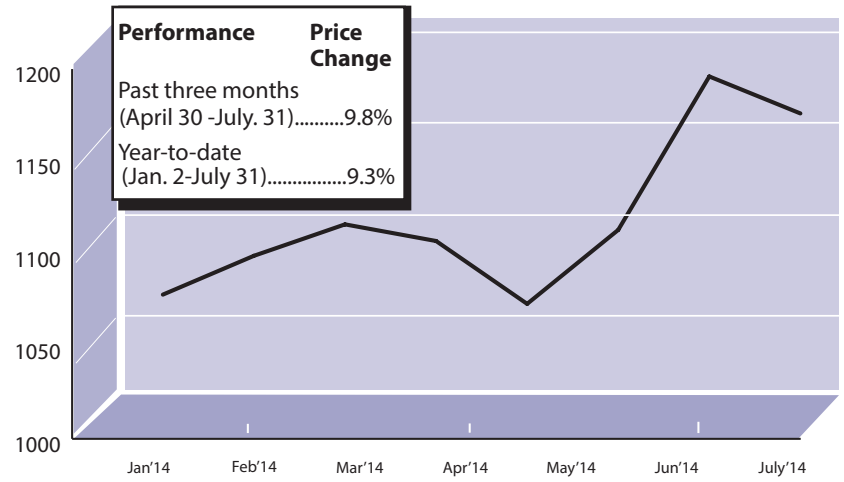
The G2 Diagnostic Stock Index gained over 9 percent for the first half of the year (Jan. 2 to July 31). Ten stocks increased for the period, while five stocks lost ground. The G2 Diagnostic Stock Index outperformed the broader stock markets so far this year, topping the Nasdaq and Standard & Poor's (S&P) 5 percent gains over the period.

The G2 Diagnostic Stock Index's outperformance of the Nasdaq and S&P was carried by seven stocks experiencing strong double-digit gains, including large companies Abaxis, Abbott Laboratories, Illumina, and Johnson & Johnson, as well as two smaller companies, Orasure Technologies and Sequenom.

The biggest gainer so far this year was **Sequenom** (San Diego), whose stock is up 61 percent year-to-date. At the end of July, the company reported second-quarter total revenue of $39.8 million, an increase of 62 percent over the second quarter of 2013. Over the same periods, total patient samples increased 7 percent to reach 50,100 accessioned, with the majority accounted for by the MaterniT21 PLUS test. While the new molecular pathology diagnostic codes had previously affected Sequenom's reimbursement, the company reports that as of June 30, 140 million lives are covered for the MaterniT21 PLUS test. Agreements are in place for three of the top five national payers as well as with Medicaid programs in 15 states.

Despite the reporting of some positive financial news, the stock of **Cepheid** (Sunnyvale, Calif.) slid 18 percent year-to-date in 2014. In mid-July the company reported revenue of $116.5 million, a jump of 21 percent the same quarter one year ago. However, Cepheid's net loss widened with the company reporting a loss of 14 cents per share, compared to 8 cents per share a year ago. The company still expects total revenue in the range of $452 million to $461 million, but an earnings loss of 51 cents to 54 cents per share for the full year 2014. The revenue targets reflect strong clinical segment performance and better-than-expected High Burden Developing Countries sales for GeneXpert systems, which now total 7,096 systems placed worldwide as of June 30.

G2 Diagnostic Stock Index



Source: The G2 Diagnostic Stock Index is tabulated by DTET *from the average percentage change in the stock price of 15 IVD companies.*

Up	Price	% Chg
Abaxis	$47.41	19%
Abbott Labs	42.12	12
Affymetrix	8.60	2
Alere	40.00	11
Becton Dickinson	116.24	7
Illumina	159.91	45
Johnson & Johnson	100.09	11
OraSure	8.23	27
Qiagen	24.43	4
Sequenom	3.75	61
Down		
Bio-Rad	114.85	-6%
Cepheid	37.64	-18
Luminex	18.20	-3
Meridian	19.71	-22
Quidel	23.87	-19

G2 Insider

Routine Inpatient Blood Draws at Midnight Improve Lab Workflow . . . Changing routine inpatient blood draws to occur at midnight, rather than in the early morning, balances laboratory workload and improves the availability of test results, according to a study published in the June issue of the *American Journal of Clinical Pathology*. From a laboratory perspective, the researchers say that redesigning inflow of laboratory orders improves laboratory processing efficiency and cuts stat orders.

Turnaround times and ordering practices were compared during an intervention period from Nov. 16 to 30, 2011, in which the researchers changed the timing of routine blood draws from the standard practice of early morning (6 a.m.) to midnight on five inpatient wards (160 bed capacity) to usual care during an observation period the prior weeks (Nov. 1 to 15, 2011). Previous evidence has shown that delayed reporting of early morning test results can lead to duplicate test orders and increases in the number of STAT orders. Additionally, it is documented from a workflow perspective that routine morning blood draws create an uneven workload distribution for the laboratory.

The researchers found that altering the blood draw time changed the total volume of laboratory test orders from 4 a.m. to 8 a.m. for the entire institution from 55 percent to 39 percent, while total volumes increased from 12 percent to 30 percent from midnight to 4 a.m. Over the intervention period, STAT orders per day also decreased significantly (344 to 301). During the second week of the intervention (Nov. 22 to 30 following a process improvement in labeling that was implemented), morning blood specimen turnaround time decreased by 41.5 minutes compared with the observation period, which also cut delivery time by 27.2 minutes and processing time by 13.5 minutes. Similar cuts in total turnaround time and delivery time were seen for midnight specimens (decreases of 155.1 minutes and 169.8 minutes, respectively) following the labeling improvements.

"Some physicians may feel that midnight blood test results are too old and order repeat tests in the morning. Our results, however, did not show any evidence of additional laboratory ordering," write the authors, led by Atsushi Sorita, M.D., then at Beth Israel Medical Center in New York. "A second unfounded concern," they write, is that "abnormal test results may not be noticed in a timely manner if the ordering physician did not review them until the morning. Our hospital has overnight physician coverage and the laboratory reports highly abnormal values to the staff immediately."

The authors conclude that this change in time of routine inpatient blood draws is both feasible and acceptable to patients and providers and may have "significant implications for hospital resource management."

Company References

AdvaMedDx
202-783-8700

Ambry Genetics
949-900-5500

American Clinical Laboratory Association
202-637-9466

Cepheid
408-541-4191

eMERGE Network
615-343-0121

Foundation Medicine
617-418-2200

NextCODE Health
617-712-1417

Nodality 650-827-8000

Qiagen 800-362-7737

Repeat Diagnostics
604-985-2609

St. Jude Children's Research Hospital
901-595-3663

Sequenom 858-202-9000

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