G2 INTELLIGENCE

Diagnostic Testing & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

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Supercomputer Dramatically Speeds Genome Analysis

The limited ability to analyze multiple genomes simultaneously creates a computational or data bottleneck that increases the time and cost of analysis, limiting the application of next-generation sequencing in the clinical environment. But this spring, researchers from the University of Chicago report adapting a Cray XE6 supercomputer to achieve the parallelization required for concurrent multiple genome analysis.

The system, they say, has the capacity to align and call variants on 240 whole genomes in approximately 50 hours. The supercomputer, in combination with publicly available software, not only markedly speeds computational time but also results in increased accuracy and usability of the sequence per genome. Named Beagle, the supercomputer is housed at Argonne National Laboratory outside Chicago.

"Improving analysis through both speed and accuracy reduces the price per genome," said Elizabeth McNally, the director of the Cardiovascular Genetics Clinic at the University of Chicago Medicine in a statement. "With this approach, the price for analyzing an entire genome is less than the cost of looking at just a fraction of genome. New technology promises to bring the costs of sequencing down to around $1,000 per genome. Our goal is get the cost of analysis down into that range."

With this computer power and price point, the researchers say, it will make it more effective to sequence the entire genome than to order 50 to 70 genes, as McNally does in cardiology practice. For more information on how information technology and software are enabling enhanced clinical use of next-generation sequencing results, please see *Inside the Diagnostics Industry* on page 5.

Pap Testing Volumes Unlikely to Decline Soon, Even With HPV First-Line Approval

Will the U.S. Food and Drug Administration (FDA's) recent approval of Roche Molecular System's cobas HPV (human papillomavirus) test as a first-line, primary screening test for cervical cancer cause Pap (Papanicolaou) test volumes to plummet? Not likely any time soon, according to the experts *DTET* spoke to.

Roche's cobas HPV, the first FDA-approved HPV DNA test, provides individual detection of HPV 16 and HPV 18, the two most common types of infection, together responsible for about 70 percent of cervical cancer, as well as pooled detection for 12 other high-risk types. This expanded indication allows for the test to be used instead of Pap testing to screen for cervical cancer in women

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25 years old and older. According to the approval, women who test positive for HPV 16 or 18 should have a colposcopy, while women who test positive for one of the other high-risk HPV types should have a Pap test to determine if a colposcopy is needed.

This approval conflicts with current professional practice guidelines, which call for the HPV test as a follow-up test for patients aged 21 and older with abnormal cervical cytology and as an adjunct test to Pap in women 30 years and older. Public comments during the time of the FDA review indicated that professional organizations' opinions are divided about use of HPV as a primary screening test. While acknowledging that HPV has superior sensitivity over Pap (an estimated 90 percent versus 50 percent), Pap testing is widely engrained in clinical practice. According to G2 Intelligence, Pap smears constitute the largest volume of testing in the anatomic pathology sector, accounting for nearly one-quarter of pathology test volume in 2012 (*U.S. Clinical Laboratory and Pathology Testing 2013-2015*).

"HPV tests are very, very good at detecting disease. It was approved because it is effective," explains Debra Papa, M.D., an assistant professor of obstetrics and gynecology at the University of Massachusetts Medical School (Worcester). "The dissent is centered around how do we use this tool." Experts, including those from the U.S. Centers for Disease Control and Prevention, tell *DTET* that any changes in practice are unlikely prior to a review of the data by professional organizations. Even then, if incorporated into practice guidelines, adoption will be gradual, with no big changes expected in the next three to five years, Papa says.

The unknowns that clinicians are waiting for research and professional societies to address include:

- **Patient-Focused Factors**—Will women object to being screened for a sexually transmitted infection? Are women comfortable with longer screening intervals?
- **Physicians' Habits**—If adopted into clinical practice guidelines, will physicians change their behavior in dropping Pap testing and expanding screening intervals to five years? Some research has shown that current guidelines expanding screening intervals have been slow to be implemented.
- **Clinical Factors**—The American College of Obstetricians and Gynecologists, in its statement to the FDA during the HPV approval process, highlighted four areas of uncertainty that are not yet fully addressed. Is HPV testing appropriate screening in women younger than 25? What is the appropriate interval for repeat testing? What are the criteria for ending screening? How to transition patients previously screened with the Pap smear alone or cotesting?
- **Financial Factors**—HPV testing is more costly (an estimated three times the difference; $50 Pap versus $150 for viral DNA HPV test). Will both payers and individuals be willing to pay for this difference? Will HPV testing be more cost-effective when considering downstream costs or will the lower specificity create higher follow-up testing, including colposcopy? A forthcoming paper by Warner Huh, M.D., of the University of Alabama Birmingham, will address some of the cost implications of HPV DNA testing.

Takeaway: Despite the recent approval of HPV testing as a first-line screen for cervical cancer, Pap testing volumes will not decrease any time soon. Professional organizations will begin considering how to incorporate this approval into practice guidelines and will begin to address many unanswered clinical questions. G2

Testosterone Testing Increasing Dramatically; Reference Range, Technological Standardization Remain Challenges

Testosterone testing has increased dramatically in the United States over the last decade, but this increase has largely been among men with normal levels, according to a study published in the March issue of the *Journal of Clinical Endocrinology & Metabolism* (*JCEM*).

This surge may be due to increased marketing efforts by supplement makers and wider recognition of naturally declining testosterone levels in older men, particularly in those who are obese or with chronic disease. However, these tests may be of limited clinical value, and there are calls for technological improvements on the part of laboratories to improve the reliability of biochemical diagnosis of hypogonadism.

While testosterone treatment is recognized for men with diagnosed hypogonadism, controversy exists over the necessity and safety of treating men who may have decreasing testosterone levels without meeting diagnostic criteria for hypogonadism. Diagnosis is confounded by a lack of agreement over the range defining testosterone deficiency, particularly at the lower normal range (200 to 350 ng/dL). Testosterone assay reference ranges have frequently been determined in populations of healthy, younger men, which may not be applicable to older men experiencing natural age-related declines. Furthermore, interpretation of results is complicated by assay variation between testing facilities.

"Heavy direct-to-consumer marketing of newer testosterone formulations in the United States may have led to a much wider interest in testosterone levels and hypogonadism symptoms, resulting in wider testing of men with nonspecific symptoms but normal levels rather than targeted testing of symptomatic individuals."
—J. Bradley Laton, Ph.D., and colleagues

In the *JCEM* study the researchers evaluated commercial and Medicare insurance claims from the United States (MarketScan Commercial Claims and Encounters and Medicare Supplementary and Coordination of Benefit databases for 410,019 men) and general practitioner health care records from the United Kingdom (Clinical Practice Research Datalink registry for 6,858 men) from 2000 through 2011. For a subset of patients for whom outpatient laboratory assays were processed by a large national lab, assay results were available (2007 to 2011) and were classified using the following reference ranges: low, <300 mg/dL (10.4 nmol/L); normal, 300 to 849 ng/dL (10.4 to 25.4 nmol/L); and high, ≥850 ng/dL (29.5 nmol/L).

The researchers found that testing has increased dramatically over the last decade in both the United States and the United Kingdom (from 39.6 per 10,000 person-years in 2000 to 170 per 10,000 person-years in 2010 in the United States and from three per 10,000 person-years to 46.4 per 10,000 person-years in the United Kingdom over the same period). However, testing in the United States is often performed in men at normal levels, with the proportion of normal results increasing from 2007 to 2011 from 64.5 percent to 73.2 percent. By contrast, in the United Kingdom testing increasingly identified men with low levels, as seen by the increase from 18.9 percent in 2000 to 26.7 percent in 2011.

Additionally, the researchers found that many men initiate testosterone treatment without recent testing. In the United Kingdom, 53.8 percent of treatment initiators

did not have a total testosterone measurement in the 180 days before initiation (32.7 percent had one test), while in the United States, 40.2 percent of initiators did not have a baseline test and 50 percent had one test.

"Heavy direct-to-consumer marketing of newer testosterone formulations in the United States may have led to a much wider interest in testosterone levels and hypogonadism symptoms, resulting in wider testing of men with nonspecific symptoms but normal levels rather than targeted testing of symptomatic individuals," write the authors, led by J. Bradley Laton, Ph.D., from University of North Carolina at Chapel Hill.

This proliferation of testing, particularly in men with a borderline medical indication for treatment, is complicated by technical difficulties that continue to plague testosterone measurement, according to a review published online in *Urology* on Feb. 17. The difficulties include the failure to establish clinically relevant normal assay ranges and harmonization of assay performance across different platforms.

Serum testosterone levels vary widely and are subject to temporal variation, as well as impact from certain illnesses, medications, and risk factors, including nutrition, alcohol consumption, and smoking. Assays vary in their performance characteristics and limits of detection, as well as normal ranges based on variation in populations utilized to derive these ranges.

"There is no large population-based study of testosterone values from healthy, fertile men with normal sexual activity and reproductive function assessed by commonly accepted validation methods," write the review authors, led by Darius Paduch, M.D., Ph.D., from Weill Cornell Medical College (New York City). "The lack of these types of studies confuses clinical decision making and impairs comparison of assays on the same subject obtained in different laboratories."

A collaborative between the American Urological Association, the Endocrine Society, and the U.S. Centers for Disease Control and Prevention is under way to optimize assay platforms and to create evidence-based normal assay ranges to guide clinical decisionmaking.

"Until such standardization is commonplace in clinical laboratories, the decision to treat should be based on the presence of signs and symptoms in addition to serum testosterone measurements. Rigid interpretation of T ranges should not dictate clinical decision making or define coverage of treatment by third party payers," the authors write. "We encourage urologists and andrologists to discuss methodology and source of reference values with laboratory directors at their institutions to better understand limitations and advantages of local assays and to improve patient care."

Takeaway: While testosterone testing has increased dramatically over the past decade, these measurements, particularly in borderline low cases, may be of questionable clinical utility until improvements in the standardization of testosterone testing are implemented.

G2 INTELLIGENCE
Inside the Diagnostics Industry

Software Tailors NGS Results for Maximum Clinical Utility

Jonathan Hirsch, Syapse founder and president

Software maker Syapse (Palo Alto, Calif.) is on a mission to bring best-in-practice software to the genomics industry.

Syapse has developed a software platform that serves as a functional bridge between laboratory information systems (LISs) and electronic medical records (EMRs). Syapse software allows labs and care providers to provide interactive molecular diagnostic test reports and decision support to providers across the clinical spectrum—from genetic counselors to oncologists or primary care physicians and even directly to patients. The software can aggregate omics, medical history, and outcomes data, and connect to third-party commercial interpretation providers, as well as public and open databases, such as ClinVar, COSMIC, PhenoDB, and OMIM. It can also accommodate clients' proprietary knowledge and care pathways.

DTET recently spoke with Jonathan Hirsch, the founder and president of Syapse, to understand how Syapse's software can expedite the transition of molecular diagnostics and next-generation sequencing (NGS) into routine clinical practice and how the software can enhance the value proposition of NGS-based testing.

The quantity of data generated from NGS-based testing is often cited as a barrier to clinical adoption. How does Syapse help alleviate this data bottleneck?

Syapse is, at the end of the day, a software company that is bringing best-practice Web-application software to the clinical genomics industry. Labs are living in a world where Excel spreadsheets, FileMaker Pro, and similar tools are what people use on a daily basis to manage their data. Our goal has been to bring the modern enterprise software revolution, which has changed how every other industry stores, interrogates, and reports on high-volume, mission-critical data, into the medical world. Syapse software can store high-volume, post-analytical omics data, pair it with clinical data, and help with the clinical reporting of molecular tests. It can also aid in clinical decision support based on the tests.

How does Syapse's platform bring together disparate IT systems?

You cannot take complex molecular test information, shove it in an electronic medical record, and hope to do anything productive with it. EMR systems are not designed for this. If you think about it, other specialized disciplines, like radiology, have their own systems—their own set of software that acts as their primary workbench. So, in this new area of omics and precision medicine, Syapse is a new class of software that can become the health care provider's omics data platform and workbench. Syapse takes over where the LIS and EMR leave off and brings data from the laboratory to the point of clinical use.

Everyone defines LIS differently, and that is part of problem. In our view, the LIS is just lab workflow. A sample comes in, you put it through a prep process, and then it goes on to the sequencer or some other assay technology. What happens after that? You get your results off the sequencer and out of the analytical pipeline, and typically the lab is taking that information and putting it into a spreadsheet or Word document. Our role in the process picks up after the analytical system leaves off, taking the post-analytical assay results to the point where you have a clinical report physicians will use. No longer will that be a Word document printed out,

faxed to the physician's desk, and scanned into the EMR as an image. We are taking that process and putting a modern piece of software around it so that at every single stage you are preserving the data in a richly structured format.

How does this data improve doctors' understanding of molecular test results?
With a faxed piece of paper, you have basically sent the physician a flat piece of information that cannot be reinterpreted or visualized differently for different physician types. However, if delivered through software, you can take that same genetic information, reinterpret it using knowledge that reflects the physician's world view, update interpretation over time as new knowledge emerges, and enable physicians who are knowledgeable about genetics to drill into details and explore the data. Most importantly, you can add clinical context to the genetic data. If the patient sees their cardiologist, the cardiologist may want to know about risk factors for cardiovascular disease, pharmacogenomics, and other clinically relevant genetic information that may not have been the target of the original test.

Who is your client? What is the business case for using this type of software?
We have two types of clients: testing labs and care providers. We are seeing tremendous adoption by hospitals, clinics, and other physician groups. Physicians are saying, we want molecular information, but we don't want that piece of paper and we don't want it in an EMR.

The basic business use case is one of efficiency and automation, which is particularly important given cuts to reimbursement. This argues for automation and reducing manual labor, while increasing volume. If Syapse software can help you do five to 10 times the test volume without increasing labor, you come out on top. Another value to the lab is that physicians are demanding better reporting tools from laboratories, and now you have the requirement for patients to be able to access test results. Perhaps most critically, provider organizations are demanding the receipt of molecular test data as structured data in standard formats, a critical component of the next phase of meaningful use. PDF files and faxes will not cut it. All of these trends are playing in our favor.

"With a faxed piece of paper, you have basically sent the physician a flat piece of information that cannot be reinterpreted or visualized differently for different physician types."
—Jonathan Hirsch

On the physician and hospital side, what we are seeing is that clinicians are ordering expensive tests, and they want to understand the clinical utility and cost-effectiveness of the data these tests provide. They want to be able to reuse test data whenever possible to get more clinical utility out of that single test. We are seeing a time efficiency argument for physicians as well. Difficult-to-use EMRs have cut into the physician's available time; they are being inundated by ever more data led by molecular information, and so they seek out other systems to help them efficiently utilize complex omics data.

How can this type of platform aid physicians and labs in meeting new requirements for direct patient access to lab results?
Our software is very good at not just storing and reporting on complex molecular information, but providing different views of that information to different types of clinicians. That same philosophy and underlying capability then extends to patients. You may want, or now need, to enable your patient to view the results of

molecular testing. Syapse software can take the same molecular test data you are reporting out and provide it in different views for the physician and patient. Our software can also package the results with different explanatory language that is more appropriate for patients. This is all at the discretion of labs and physicians as to whether and how they want to implement this using Syapse software, but the writing is on the wall as far as patient access goes.

What is Syapse's role in bringing NGS into routine clinical practice?
There are factors that have little to do with us that are advancing the clinical genomics industry, primary among them is that the sequencers are not just getting cheaper, but they are getting far easier to use. Some would say we are already at the point where you can place a sequencer in a molecular pathology laboratory in a hospital and the hospital can do molecular testing internally, just like they do their IHC, FISH, and other standard assays. We are seeing this trend in hospitals across the country. The era of sequencing being done only in specialized, send-out laboratories is quickly coming to an end. We are seeing it become pervasive throughout the medical system, which means that testing is being repatriated and brought back into the hospital labs.

Our role at Syapse in pushing forward the clinical use of omics is providing a software ecosystem so that the molecular pathology lab at every single hospital can have the same software power as a large reference lab with infinite software resources at their disposal. The challenge is less in the lab workflow and more in solving the problem of how to bring sequencing results directly to the physician in a way that they can make sense of, and for the provider organization, pairing sequencing data with outcome and cost information. We are shifting to a point where clinical utility of test results is the central problem, not data generation. That is where Syapse provides the most differentiated value: enabling physician utility of testing and building your evidence base for clinical utility.

The myriad of available data sets helps in the clinical interpretation of these complex test results. How does Syapse keep up with this rapidly changing knowledge base?
We are very customer- and user-focused. We are not going to tell the laboratory professional which data sets and what interpretive resources to use. Our job is to make it really easy to connect to any interpretive systems or public databases that you, as the lab professional or physician, want to use. You can make that determination as to what you feel is the most accurate or applicable resource. Syapse will then provide robust software interfaces and automation to connect to and integrate those interpretive knowledge sets. The other thing we are doing is working with hospitals and labs to enable knowledge-sharing networks, so that collaborating organizations using our software can share interpretive information seamlessly. So far, our customers have told us that this is a great approach to aggregating knowledge so that hospitals and laboratories are working off the same knowledge set that they and their collaborators contribute to, rather than each one reinventing the wheel every time they want to spin up a new molecular test.

Syapse By-the-Numbers

Year Founded: 2008

Medical Concepts in Syapse Data Graph: 20,000

Data Sources Integrated per Customer: 10

Input Data Volume for Molecular Test Report: 500 megabytes to 10 gigabytes

Report Generation Time: 1/1000th standard methods, achieved through software automation

Adoption of Pharmacogenomic Testing in Psychiatry Slow; Experts Point to Lack of Evidence, Cost-Effectiveness

Despite the hope that personalized medicine can improve care in a notoriously difficult to treat patient population, pharmacogenomic testing in the field of psychiatry is still characterized by clinicians as an emerging technology. Commercially available tests developed by startup personalized medicine companies are emerging, as are in-house tests developed by large hospitals and laboratories. But clinical experts in the field say the tests, which are a big improvement over trial-and-error medication selection, have not yet fulfilled the dreams of truly personalized psychiatric care.

"The tests available to individual practitioners really do seem to have value, but where we are at the present time is that tests are really aiding drug selection based on pharmacokinetics. Current testing cannot yet predict responsiveness, but they really are a substantial step forward," says Daniel Hall-Flavin, M.D., an assistant professor of psychiatry at the Mayo Clinic in Rochester, Minn., who has participated in translational research efforts with pharmacogenomic firm AssureRx (Mason, Ohio).

> ***"I liken it to the New York City subway. There are just so many stops, so many factors influencing how individuals respond to drugs. Pharmacokinetics may be an express stop, but it is just one stop."***
> ***—Daniel Hall-Flavin, M.D., Mayo Clinic***

Trials of these early versions of pharmacogenomic tests demonstrate that these assays can enhance the safety of prescribing psychotropic medications by cutting potential adverse drug reactions and can decrease the time and cost in initiating successful treatment, particularly for patients with depression. However, the genetic knowledge gained from pharmacogenomic testing is not foolproof, as genetics is an important factor but not the sole determinant of a treatment's effectiveness.

Genetics Is Just One Consideration

Drug response phenotypes are influenced by the complex intersection of genetics and the environment, which can include such factors as diet, smoking, and other medications.

"There are so many considerations, I liken it to the New York City subway," Hall-Flavin tells *DTET*. "There are just so many stops, so many factors influencing how individuals respond to drugs. Pharmacokinetics may be an express stop, but it is just one stop. So it is important to consider, but it is not the whole picture or the whole patient."

But advocates for pharmacogenomic testing say that it does improve care. For example, Hall-Flavin explains that when starting treatment selection with a patient with depression, there are more than 25 antidepressants to choose from. On average there is a 30 percent to 40 percent chance the patient will respond to the first medication and a two-thirds to three-quarter chance that they will respond

to some medication combination. Genetic data examining the metabolic enzyme CYP2D6 show that in the general population of Caucasians, 7 percent to 8 percent will be poor metabolizers while another 7 percent to 8 percent will fall on the opposite end of the spectrum and will be rapid metabolizers. Hall-Flavin says it is in these patients on the ends of the spectrum that the pharmacokinetic information on an individual's drug metabolism qualities makes the biggest impact. Personally, he says he generally utilizes pharmacogenomic testing in complex patients—either those who have not responded to previous treatment selections and truly have difficult to treat depression and those who are medically difficult and are taking multiple other medications, where drug-drug interactions are a concern.

Driving Adoption

"We often lose sight in medicine that these are new products in new markets. We would see similar patterns of adoption if you compare [pharmacogenomic tests] to new technology in other industries," says Nancy Grden, the general manager at the pharmacogenomics firm Genomind (Chalfont, Pa.). "Fundamentally there are early adopters, there is a group who will never adopt it, and there is a large middle group that needs to see data and know that their colleagues are using it. This is a normal part of adoption for all new products."

The profile of Genomind's early adopters includes psychopharmacologists, many of whom are largely already aware of the research but didn't have access to a commercial test. More encouraging to the company is test adoption by psychiatric nurse practitioners, who Grden says are on the front lines every day and are happy to have a new tool in their arsenal. Other common factors among early adopters of Genomind's Genecept assay include outpatient and hospital systems with more difficult to treat patients, including those with longer lengths of stay, as well as those who see more self-pay patients.

> ***"Fundamentally there are early adopters, there is a group who will never adopt it, and there is a large middle group that needs to see data and know that their colleagues are using it. This is a normal part of adoption for all new products."***
> ***—Nancy Grden, Genomind***

But test developers are currently trying to penetrate that big group of psychiatrists who really need more evidence on the benefits of pharmacogenomic testing before widespread clinical adoption will take off.

Experts *DTET* spoke to point to several actions that laboratories and test developers need to undertake to both have the necessary evidence these providers expect to see and to present the tests' information in an actionable format. For one, test developers need to continue to develop a larger body of evidence, employing high-quality study methodologies. These physicians are looking for randomized, controlled trials demonstrating that pharmacogenomic testing provides clinical benefits to the patients and can make their own practice more efficient with test utilization.

Part of the exhibition of data literally includes a presentation component—the user interface for test results. Can psychiatrists easily comprehend what to do with the results? Are the results tied to actionable clinical decision support? Hall-Flavin emphasizes the importance of presenting results in an understandable way for

busy physicians who may only have 10 minutes to 15 minutes with each patient. Additionally, the test results need to be communicated to patients with no genetic background, and laboratories can assist with providing that format.

To realize increased test adoption, laboratories and test developers also need to push for some larger, systemwide changes. For instance, Hall-Flavin says the broader research community needs to better "slice and dice" psychiatric phenotypes, which tend to be very heterogeneous collections of symptoms. These efforts will be enhanced by improved electronic medical record functionality including data mining using natural language processes that can better characterize responsiveness in very specific phenotypes.

Commercially Available Pharmacogenomic Assay for Psychiatry

AssureRx Health (Mason, Ohio): GeneSightRx assay

The company's pharmacogenomic technology is based on intellectual property licensed from the Mayo Clinic and Cincinnati Children's Hospital Medical Center. The company's GeneSight line of laboratory-developed tests (GeneSight Psychotropic, GeneSight ADHD, GeneSight Analgesic) analyze variants affecting the metabolism and response to psychiatric medications and are intended to serve as a clinical support tool in making treatment decisions.

The company's latest publication, a double-blind randomized control trial published in November 2013 in *Discovery Medicine*, shows that patients whose treatment decisions were pharmacogenomic-informed were more than twice as likely to respond when treatment was guided by GeneSight compared to treatment as usual. This effect was most dramatically seen in the 30 percent of patients identified by the test to have severe gene-drug interactions.

The GeneSight clinical report utilizes a binning method. The patient's genotype is determined for each of the six genes in the panel. A composite phenotype for each drug is created based on the phenotypes predicted from each of the six genotypes. The 18 most commonly prescribed antidepressants and eight antipsychotics on the panel are positioned in a green, yellow, or red "bin."

Genomind (Chalfont, Pa.): Genecept assay

Genomind's Genecept assay is a saliva-based panel that includes a patented algorithm for analysis of 10 genes, including pharmokinetic genes related to drug metabolism (CYP2D6, CYP2C19, CYP3A4), as well as pharmacogynamic genes tied to serotonin transporters and receptors, gated calcium channels, ankyrin G, dopamine receptors, catechol methyl transferase, and methylenetetrahydrofolate reductase.

Grden tells *DTET* that the list price (self-pay with a credit card) is $650, which includes a clinician consult with a psychopharmacologist. The company also has a patient assistance plan and commercial insurance reimbursement.

In early April the company closed a $5 million round of Series A financing, led by Claritas Capital, to fund growth in commercialization of the assay.

Broader efforts are also needed to improve clinician education when it comes to genomics. Physicians continue to self-report perceived deficits in their knowledge of when to order genetic tests and how to interpret genetic tests, which will both prove to be barriers to wider use of molecular technologies.

Researchers from Columbia University surveyed psychiatrists to gauge familiarity and comfort with ordering and interpreting genetic tests. According to the study results, published in the April issue of the *Journal of Genetic Counseling*, 14 percent of 372 responding psychiatrists had ordered genetic testing in the past six months. These orders included pharmacogenomic tests but also tests to diagnose learning disabilities and dementia. Only one-third of respondents felt confident about how to order and where to send genetic tests, and less than one-quarter of responding psychiatrists had a genetics professional to whom to refer patients.

Laboratories can play a critical role in providing continuing medical education programs and other professional development for psychiatrists. Additionally, advocating for development of clinical practice guidelines that incorporate genomic testing and the inclusion of pharmacogenomic information in electronic medical records will also aid in improving physicians' comfort with handling these test results.

Other stakeholders, including payers, will also influence test adoption. Evidence that the cost of pharmacogenetic testing is justified by clinical outcomes is lacking, and greater efforts are needed to generate comparative effectiveness data. Not only are there the direct treatment costs, but the financial burden of treatment failures can be substantial in terms of disability claims, decreased productivity, and missed work, resulting from less than optimal therapy.

Pharmacogenomic Biomarkers in Psychiatric Drug Labeling
Psychiatric Drugs With Warnings and Precautions/Dosage Administration

Drug	Marker	Referenced Subgroup
Aripiprazole	CYP2D6	CYP2D6 poor metabolizers (dosage only)
Atomoxetine	CYP2D6	CYP2D6 poor metabolizers
Fluoxetine	CYP2D6	CYP2D6 poor metabolizers (warning and precaution only)
Iloperidone	CYP2D6	CYP2D6 poor metabolizers (warning and precaution only)
Pimozide	CYP2D6	CYP2D6 poor metabolizers
Thioridazine	CYP2D6	CYP2D6 poor metabolizers (warning and precaution only)

Source: U.S. Food and Drug Administration

These data are beginning to emerge. A study, which was funded by AssureRx and published in *Translational Psychiatry* in March 2013, retrospectively demonstrated that inappropriate medication selection led to increased health care utilization and cost. For psychiatric patients whose medication status for a year was identified as having been suboptimal, there were estimated higher costs of $5,188 per individual.

These costs were derived from findings of roughly 68 percent more health care visits, greater than threefold more medical absence days, and greater than fourfold more disability claims patients whose medication regimen included a medication identified by the GeneSightRx panel as most problematic for that patient, based on genomic analysis, compared to all other patients.

Pharmacogenomic Biomarkers In Psychiatric Drug Labeling
Psychiatric Drugs With Drug Interaction Labels

Drug	Marker	Referenced Subgroup
Atomoxetine	CYP2D6	CYP2D6 poor metabolizers
Citalopram	CYP2C19	CYP2C19 poor metabolizers
Clomipramine	CYP2D6	CYP2D6 poor metabolizers
Clozapine	CYP2D6	CYP2D6 poor metabolizers
Desipramine	CYP2D6	CYP2D6 poor metabolizers
Diazepam	CYP2C19	CYP2C19 poor metabolizers
Fluvoxamine	CYP2D6	CYP2D6 poor metabolizers
Iloperidone	CYP2D6	CYP2D6 poor metabolizers
Imipramine	CYP2D6	CYP2D6 poor metabolizers
Modafinil	CYP2D6	CYP2D6 poor metabolizers
Nefazodone	CYP2D6	CYP2D6 poor metabolizers
Nortriptyline	CYP2D6	CYP2D6 poor metabolizers
Paroxetine	CYP2D6	CYP2D6 poor metabolizers
Perphenazine	CYP2D6	CYP2D6 poor metabolizers
Risperidone	CYP2D6	CYP2D6 poor metabolizers
Trimipramine	CYP2D6	CYP2D6 poor metabolizers
Venlafaxine	CYP2D6	CYP2D6 poor metabolizers

Source: U.S. Food and Drug Administration

Additionally, Genomind presented new data at the International Society for CNS Clinical Trials and Methodology Autumn Conference (Sept. 30-Oct. 2, 2013; Philadelphia) that patients who used the Genecept Assay had significantly increased medication adherence rates as compared to controls. This adherence translated to a relative cost savings of 9.5 percent over the four-month trial period (roughly equal to an annual cost savings of $1,827 per patient).

Takeaway: Hope for personalized psychiatric care is still outpacing the current generation of pharmacogenomics tests. These tests, though, are permeating clinics, particularly for use in complex patients. Evidence is emerging that these tests can improve the safety profile of medications prescribed for psychiatric patients, but widespread adoption will be hampered if strides are not made in producing solid evidence of the outcomes and cost-effectiveness benefits of these tests.

Interest Continues in CDx Codevelopment, But Clinical Utility Focus Needed

A recent string of announcements of partnerships aimed at expanding companion diagnostic (CDx) codevelopment reflects the commitment of pharmaceutical companies to develop targeted therapeutics, particularly for their cancer product pipelines. Yet for these tests to be commercially successful, experts say test developers must incorporate a steadfast focus on the tests' clinical utility during all stages of development.

The 1998 Herceptin/HercepTest approval for metastatic breast cancer marked the beginning of the era of CDx codevelopment. While there has been tremendous hope that such targeted therapeutics will increase the efficacy of cancer treatment and improve survival outcomes, there remains a limited number of approved CDx on the commercial market.

"People said [HercepTest] was heralding in a new age—the way of the future. But another decade passed and right now we have relatively few CDx, leaving a lot of people asking what happened," Kenneth Emancipator, M.D., a board member of the American Society for Clinical Pathology, explains to *DTET*. "But when you look at pharmaceutical companies' current pipelines, I predict an explosion of CDx within five years."

Experts say demonstration of a test's clinical utility is key to overcoming several large hurdles, namely reimbursement and regulatory approval, on the path to clinical adoption of companion diagnostics. CDx codevelopment was the topic of a special focus issue of *Clinical Cancer Research* (*CCR*) published online March 14. The authors of one of the articles stress that demonstration of clinical utility should be incorporated into the early stages of assay development and trials "by anticipating what types of questions will need to be answered and what kinds of data need to be generated to supplement routine analytical and clinical validation studies."

According to David Parkinson from New Enterprise Associates (Menlo Park, Calif.) and colleagues, the best practices for demonstration of clinical utility incorporate these steps:

- Define the intended use of the assay along and understand the clinical context of the test;
- Begin outlining what evidence will be needed early in assay development and project planning;
- Evaluate potential regulatory pathways and accompanying business strategy needs;
- Integrate all steps needed to demonstrate clinical utility (both pre- and post-approval) into the development plan;
- Design clinical trials to begin gathering evidence of clinical utility even before approval and commercialization; and
- Assemble the chain of evidence.

This additional evidence needed to establish clinical utility is, of course, costly to produce and adds to the inherent risk in developing CDx products.

Questions to Evaluate Clinical Utility

- Does the test improve clinical and health outcomes because of the result's subsequent effect on diagnosis and intervention?
- Do the results provide information useful for decisionmaking?
- Do the benefits outweigh the harms when the test results are considered in patient management?
- Is there a chain of evidence demonstrating that the test results can change patient management decisions and improve net health outcomes?

Source: Adapted from "Evidence of Clinical Utility: An Unmet Need in Molecular Diagnostics for Patients With Cancer" by David R. Parkinson, Robert T. McCormack, Susan M. Keating, et al., published in Clinical Cancer Research *online March 15.*

"A CDx is a low-margin profit that assumes pharmaceutical risk in development," says Emancipator. "Pharmaceutical risk with a diagnostic [financial] reward is not a good deal. . . . Even with pharmaceutical companies paying for a portion of the research and development, there is an opportunity cost for the diagnostic company. What if the drug fails and doesn't make it to market?"

Even if the drug-CDx pair does make it to the market, test reimbursement can remain a challenge. Diagnostic tests are notoriously undervalued by payers and are not reimbursed according to the value of the information they provide.

2014 Announcements of CDx Partnerships

Diagnostic Co.	Pharmaceutical Co.	Partnership Details
Agendia	Daiichi Sankyo	The Japanese drug maker announced in late April it will use Agendia's oncology biomarker technology to evaluate new drugs in clinical trials.
Diaxonhit	InnaVirVax	Diaxonhit received $2.4 million to develop a CDx for an AIDS vaccine and personalized care of AIDS patients from InnaVirVax, in conjunction with the Strategic Industrial Innovation Program (France), in late April.
Ventana (a Roche company)	Genmab	Ventana will develop an immunochemistry CDx that could be used for screening tissue factor from solid tumor samples in patients participating in clinical trials for investigational drug HuMax-TF-ADC.
Prestizia (France)	Splicos and CNRS	In collaboration with the French National Center for Scientific Research, Prestizia will develop a microRNA CDx for the investigational HIV treatment SPL-464.
Eutropics	Tolero Pharmaceuticals	Eutropics announced in January it will use its Praedicare-Dx biomarker platform to support the development of Tolero's alvocidibm, in Phase III trials, for patients with two forms of leukemia.
Dako collaborations (an Agilient company)	Amgen	Early in the year, Dako announced several with Amgen to work on a CDx for a drug candidate for an undisclosed form of cancer.

Source: Compiled by DTET *from press releases and news reports*

"Recognition of the importance of establishing the clinical utility of a test can be reinforced by payer resistance to tests lacking this level of evidence, or by a tiered reimbursement system which rewards clinical tests with superior levels of clinical utility information," writes Parkinson in *CCR*. "Absent a rewards system that recognizes the value of this information, complex tests of high predictive value will not be developed with the needed frequency."

Also impeding test development and adoption is a less than clear regulatory framework. The future regulatory environment for laboratory-developed tests remains uncertain, while the U.S. Food and Drug Administration's (FDA's) Elizabeth A. Mansfield describes the agency's approach to CDx approval as a "still-evolving regulatory paradigm."

"To date, no two co-development activities have been exactly the same, so the learning curve for all parties has been steep," admits Mansfield in the *CCR* special focus issue. "In its efforts to be as flexible as possible within the bounds of regulatory constraints, FDA has considered each situation individually. Although this approach allows the greatest flexibility in development, it does not lend itself easily to defining a prescriptive or predictable pathway. FDA continues to believe that although predictability is important, flexibility must take precedence."

Advances in technology are further confounding the evolving regulatory and reimbursement paradigms as next-generation sequencing (NGS) makes it possible to examine multiple genomic alterations simultaneously, seemingly making the one-test, one-drug model appear dated.

"It seems almost inevitable that a consolidation of diagnostic testing should take place, to enable a single test or a few tests to garner all the necessary information for therapeutic decision making," writes Mansfield. Yet expanded NGS, in the short term, will not dominate CDx testing.

"There are a lot people talking about next-gen as a panacea," says Emancipator, who currently works for Merck Research Labs as director of CDx. "There is definitely a place for it, as it is a way around the one-test, one-drug phenomenon, but there are other types of biomarkers that are important, too, that are not immediately available to NGS."

Takeaway: Pharmaceutical companies and test developers will keep an eye on new technologies, including NGS, to possibly improve the efficiency and cost-effectiveness of CDx testing. Regardless of the platform, CDx development needs to focus on clinical utility.

Cholesterol Screening Rates Low in Overweight, Obese Kids

Overweight and obese children are frequently not receiving recommended screening tests for obesity-related conditions, according to a study published in the April 11 issue of *Morbidity and Mortality Weekly Report*. A lack of awareness of testing-related guidelines may contribute to the low rates of utilization of these screening tests.

In response to the rise in obesity among U.S. children and adolescents from 1980 to 2010, the American Academy of Pediatrics recommended targeted laboratory screening for metabolic disorders, including lipid panel testing, among children and adolescents with a body mass index (BMI) at or above the 85th percentile based on age or presence of certain risk factors, beginning at age 10 years.

The researchers utilized data from a population of children and teens enrolled in Maryland Medicaid or the Maryland Children's Health Program to determine whether or not screenings, per the recommendations, were being performed in routine clinical practice. BMI percentiles were calculated for a random sample of 1,600 children (aged 2 years to 19 years) per year (2005 to 2010) who were seen for a well-child visit. Laboratory tests undertaken and diagnosed obesity-related conditions were identified through medical encounter records.

The researchers found that 16.5 percent of the included children were overweight (BMI from 85th to 94th percentiles) and 21.4 percent were obese (BMI of 95th percentile or above), with no significant change in the prevalence of overweight and obesity during the study period. There was a significant increase in the diagnosis of obesity-related conditions with increasing BMI, with 33.5 percent of obese participants diagnosed with asthma, 7.9 percent diagnosed with dyslipidemia, and 7.2 percent diagnosed with depression. Lipid panel tests were undertaken in only 29.9 percent of overweight and 40.2 percent of obese participants.

Co-author Cheryl De Pinto, M.D., from the Maryland Department of Health and Mental Hygiene, tells *DTET* that while noncompliance in executing lab orders may contribute to the low rates of testing, a lack of provider education about the need to test in this population may also be a contributor.

Takeaway: At-risk kids and teens are not being adequately tested for obesity-related conditions. While patient noncompliance may in part contribute to low testing rates, laboratories can work with pediatricians and other providers to ensure knowledge of obesity-related testing guidelines.

Simple Urine Test Can Detect BP Medication Noncompliance

Nonadherence to blood pressure lowering medication is common clinically (one in four) and a simple urine test can help clinicians identify these patients and potentially avoid further costly work-ups, according to a study published online April 2 in *Heart*. This urine test could potentially fill a gap by providing an objective and direct-detection clinical tool to identify hypertension therapy noncompliance and could aid in better stratifying patients needing further costly intervention.

In the present study, 208 hypertensive patients (125 new referrals, 66 follow-up patients with inadequate blood pressure control previously seen in the specialty clinic, and 17 renal denervation referrals) were evaluated for anti-hypertensive drug compliance using high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. The researchers found that one-quarter of patients were totally or partially nonadherent to anti-hypertensive treatment (total nonadherence equaled 10.1 percent; partial nonadherence equaled 14.9 percent). Follow-up patients with inadequate blood pressure control (28.8 percent) and those referred for consideration of renal denervation (23.5 percent) had the highest prevalence of nonadherence.

In 20 percent of patients non-compliant with BP medication, follow-up appointments and further testing could be avoided with a urine test to detect non-compliance.

"A majority of these [nonadherent] patients in any secondary/tertiary care center would routinely undergo many additional tests and procedures in search of the explanation for their apparent unresponsiveness to standard therapy prescribed by primary care," write the authors, led by Maciej Tomaszewski, from University of Leicester (United Kingdom). "Our data suggest that in 20 percent of such patients, these investigations (along with follow-up appointments and exposure to unnecessary additional treatment) could be potentially avoided if HP LC-MS/MS urine analysis was used as a routine screening for non-adherence."

The authors argue the advantages to a urine-based biochemical screening for therapeutic adherence holds many advantages, including that it is noninvasive and can be conducted prior to a clinic appointment (with an estimated three-hour turnaround time), it provides a clear yes-or-no answer with "excellent sensitivity" and is relatively inexpensive (approximately $50, although the cost of the analyzer can be substantial at approximately $250,000). However, the authors caution about "several imperfections" associated with such a screening tool, including that a single spot urine analysis is only a snapshot and may not give a full picture of compliance.

"Furthermore, intuitively, one might expect some patients to better adhere to treatment on the day of clinic attendance (the so-called 'tooth brush effect')," write the authors. "Further studies on utility and cost effectiveness of HP LC-MS/MS urine analysis should be conducted against indirect measures of adherence to inform future health policies and clinical practice."

Takeaway: If further study demonstrates the utility and cost-effectiveness of such a screening test, a urine-based test for common medication noncompliance could improve resource and patient management.

G2 Insider

Blood Cultures in the ER for Pneumonia Patients Rising, Despite Recommendations . . . The collection of blood cultures in patients seen in the emergency room (ER) and ultimately hospitalized with community-acquired pneumonia (CAP) continue to increase despite recommendations to reserve the test for only severe illness, according to a research letter published online March 10 in *JAMA Internal Medicine*. The authors cite nonclinical factors, but not clinical indicators, as the significant predictors of blood culture use and call for further national attention to ensure the prudent use of blood cultures in pneumonia management.

Practice guidelines were revised (2005 to 2007) in order to reflect changing sentiment regarding the limited clinical utility of routine blood cultures for all patients hospitalized with CAP. Recognizing that false-positive results from blood cultures can lead to inappropriate anti-microbial use and longer lengths of stay, modifications were made to recommendations shifting from routine culture collection to using the test only in those with severe pneumonia.

Data from the National Hospital Ambulatory Medical Care Surveys (2002 through 2004 and 2007 through 2010) were analyzed to assess patterns in utilization of cultures in adults hospitalized with CAP. For comparison, trends in culture collection in patients hospitalized for a urinary tract infection (for which recommendations did not change over the course of the study period) were also assessed.

The researchers found that the percentage of patients hospitalized with CAP who had culture collections increased significantly from 29.4 percent in 2002 to 51.1 percent in 2010, while the rates of culture for urinary tract infection remained consistent over the same period. Culture collection was not predicted by disease severity. Admission to the intensive care unit was actually associated with lower odds of obtaining cultures. Hospital ownership and region were strong predictors of culture collection.

As a possible explanation for the pattern, the authors cite the 2002 mandate by the Centers for Medicare and Medicaid Services (CMS) and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) that culture collection in the ER should occur before antibiotic administration.

"[This] may encourage providers to reflexively order cultures in all patients admitted with CAP in whom antibiotic administration is anticipated, even though cultures are strongly indicated in only the sickest patients," write the authors, led by Anil N. Makam, M.D., from University of Texas Southwestern Medical Center, Dallas. "Given rising trends in obtaining cultures in low-risk patients, we advocate for the JCAHO and CMS to reexamine this measure with consideration of eliminating it entirely to discourage overuse."

Company References

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