G2 INTELLIGENCE

Diagnostic Testing & Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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CONTENTS

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Utilization of Genetic Testing for Familial Cancers 'Disappointing'

Although there had been a steady uptick in tests performed for the breast and ovarian cancer-causing mutations BRCA1 and BRCA2, mutational testing for other familial forms of cancer have not gained significant traction—with only a third of relatives of individuals known to have either the BRCA or the Lynch syndrome MMR mutation undergoing genetic testing, according to a study presented at the European Society of Human Genetics' annual meeting (Paris; June 8-11).

The researchers analyzed data from the French National Cancer Institute (2003 to 2011). Based on 240,134 consultations over the eight-year study, the researchers found a significant and steady increase in genetic tests performed for the BRCA1/2 genes—an increase from 2,095 to 7,393 tests per year. The increase in testing for the MMR genes (from 1,144 to 1,635 per year) was not significant. In families with an individual identified with a BRCA1/2 or a MMR mutation, there was an average of three relatives who underwent testing.

"Given that such testing can provide many options to enable individuals to manage their cancer risk, it is vital to encourage awareness and acceptance among both the public and medical professionals," said the study's lead author, Pascal Pujol, M.D., from Montpellier University Hospital in France. "We believe that our findings would be likely to be replicated in many other countries across the world. . . . We urgently need a major program of awareness among all those concerned, involving medical education and training, information programs for patients and their families, public health campaigning, and improved genetic counseling."

For more information on how clinician awareness influences adoption of molecular testing, please see the *Special Focus* section beginning on page 8.

Gene Patent Ruling Seen as Positive for Clinical Labs, Will Likely Speed Transition to Multigene Tests

The Supreme Court's June ruling on gene patents is already opening the market for BRCA testing and is largely seen as a positive for clinical laboratories that have been blocked from entering this testing space.

In a highly anticipated, but largely expected decision, the Supreme Court unanimously decided that isolated genomic DNA (gDNA) is not eligible for patent protection. The decision in the case, *Association for Molecular Pathology v. Myriad Genetics*, authored by Justice Clarence Thomas, struck a middle

Continued on p. 2

▲ **Gene Patent Ruling Seen as Positive for Clinical Labs,** *from page 1*

ground with the court declaring isolated gDNA is an unaltered "product of nature" and thus unpatentable, but patents for complementary DNA (cDNA) are still allowable.

While the National Society of Genetic Counselors estimates that approximately 20 percent of all human genes are patented, not all of these patents are enforced and some early patents have expired. Unlike Myriad Genetics (Salt Lake City) few other commercial entities have built a sizable, testing monopoly around a single, human gene patent and thus, many predict the decision will not have wide-reaching impact but will open up the BRCA testing market.

Impact on Myriad

Many predict that Myriad will maintain its market dominance in BRCA testing in the short term, even as other laboratories rush into testing of hereditary risk for breast and ovarian cancers. Despite losing its gene patent standing, Myriad still possesses several competitive advantages.

First, the company argues it still possesses 23 patents and still has almost 500 claims around its BRCA1/2 testing franchise, including those related to primers, cDNA composition of matter, and method claims. Debate persists regarding how aggressively Myriad will pursue action against competing labs. But early indicators, including a suit filed July 9 against Ambry Genetics (Aliso Viejo, Calif.), demonstrate Myriad will take an aggressive stance. However, possibly most importantly, Myriad maintains a proprietary database that extensively catalogs variants of unknown significance (VUS) based upon its extensive testing history.

'Free the Data' Movement

Shortly after the ruling, a broad consortium of stakeholders, including Genetic Alliance, University of California San Francisco, InVitae, and patient advocates, announced the formation of Free the Data!, an initiative aimed at building a comprehensive, reference database to help in characterizing BRCA1 and BRCA2 mutations. The campaign calls for patients and physicians to enter mutations into a public access database, thereby chiseling away at Myriad's information advantage.

"While the Supreme Court's ruling has been welcomed enthusiastically by many, the Myriad case has been only a modest victory for the advocates of genetic-data sharing," wrote Eleonore Pauwels, a science and technology innovation program researcher at the Woodrow Wilson International Center, in a June 18 op-ed in the *New York Times*. "In reality, gene patents were only one part of the problem. A more vexing, and still pressing, issue is how companies withhold genetic data as a trade secret."

Analysts agree that Myriad's proprietary database not only affects the quality of results interpretation for patients, but it can also aid the company in protecting its dominant market position as new laboratories enter the market.

"We believe that Myriad's BRCA1/2 germline mutation/phenotypic database, underlying software classification algorithms, and ability to test for large genomic rearrangements and incremental markers related to hereditary breast and ovarian cancer . . . represent meaningful competitive advantages," writes Amanda Murphy, an analyst at William Blair & Co., in a research note.

Murphy estimates Myriad's database has 16,000 mutations versus the 1,000 in the public database, translating to Myriad's ability to identify the mutation and the associated breast cancer risk 98 percent of the time. Given that competing labs will initially rely on variants listed in public databases, Murphy's analysis estimates that competing labs may have mutations classified as having an unknown clinical significance 30

percent to 50 percent of the time. Some anticipate that with high rates of VUS, reflex testing may need to be sent to Myriad anyway. At a VUS rate of 20 percent, Murphy says, competing tests would have to be priced below $2,500.

"In the near term, at least, the market will pit Myriad's advantage of having a huge proprietary database built on its period of monopoly against firms promoting medical progress through data access and open science," write Arti Rai and Robert Cook-Deegan, M.D., from the Duke Institute for Genome Sciences & Policy (Durham, N.C.), in a perspective piece published online June 27 in *Science*.

Broader Commercial Effects

Despite hyped fear that prohibiting gene patents would disincent biotech companies from investing in genomic research and development, the Supreme Court's decision is largely viewed as a positive development for independent clinical labs.

Citing macro factors including Affordable Care Act, the aging population, and the effects of a more educated consumer resulting in patients taking a more active role in their health care, Charlie Miller, an analyst at Morningstar, expects BRCA testing volumes, in general, to be driven upward.

Almost immediately after the Supreme Court's decision, several laboratories announced they would begin offering genetic testing for breast and ovarian cancer risk, effectively ending Myriad's monopoly. Laboratories have announced that as soon as the end of the summer they will begin offering BRCA testing, including GeneDx (subsidiary of Bio-Reference Laboratories; Gaithersburg, Md.), Ambry Genetics, DNATraits (division of Gene By Gene; Houston), Pathway Genomics (San Diego), and Quest Diagnostics (Madison, N.J.), as well as academic institutions including the University of Washington (Seattle) and Albert Einstein College of Medicine (New York City). While not all have announced pricing, DNATraits says it will offer BRCA testing for $995.

"The gene patent decision clearly opens the door for a new market with potential benefits to revenue/volume and earnings," writes Darren Lehrich, a Deutsche Bank analyst, in a research note. He cites Myriad's 2012 revenues from BRCA testing of $405 million as a basis for sizing the opportunity. "Each of the large national labs have 10 percent to 12 percent market share of the U.S. clinical lab testing market, so the launch of a successful BRCA testing program could add 50-100 bps to revenue growth over time if their national market shares were commensurate in this arena."

But competing laboratories are not the only threat to Myriad's BRCA gene testing franchise. Single-gene tests are phasing out anyway in favor of multigene panels that can be offered for the same price. In making its announcement of offering BRCA testing, GeneDx said BRCA analysis will be part of a comprehensive inherited cancers, 27-gene panel offered at a cost comparable to single-gene testing.

"The Court's opinion not only emboldens competitors that rely on traditional sequencing methods, but also reduces the fear of infringement among those that rely on whole-genome sequencing. Among the new entries are tests not just on BRCA1/2, but also multigene tests that will now include BRCA1/2," write Rai and Cook-Deegan.

Myriad itself has recognized this trend and in early May announced its plans to phase out its BRCA gene tests by the middle of 2015 and replace them with a new multi-

hereditary 25-gene cancer panel called myRisk Hereditary Cancer. The price is expected to be similar to what the BRCA analysis costs now.

"The most obvious impact of the decision may be increased access, reduced price, and perhaps most importantly, the emergence of multigene first-line genetic tests for inherited risk of breast and ovarian cancer—replacing the current multistep process of testing first for just two genes," write Rai and Cook-Deegan. "Firms and university labs are beginning to compete on price. Myriad Genetics and other companies that have relied on gDNA patents for their service monopolies will likely have to compete on other grounds, such as turnaround time, quality of testing, clarity of clinical reports, sales force, and securing payment from insurers."

Keep an Eye on Methods Patent Cases, Expert Says

While the Supreme Court's decision does settle the legal standing of isolated gene product patents, experts predict that lower courts will soon grapple with other diagnostics-related cases including cases involving methods patents, application of knowledge about the genes, and potentially whether cDNAs are unpatentable because they are "obvious."

In a recent interview with *DTTR*, John Conley, the Kenan Professor of Law at the University of North Carolina, Chapel Hill, and editor of the *Genomics Law Report*, said that while much of the diagnostics industry's focus has been on the product patents in the *Myriad* case, patent lawyers are paying close attention to a series of method patent cases that could have a larger impact on the industry.

"Putting together Mayo and the Federal Circuits ruling in Myriad [regarding methods patents] it is increasingly difficult to get a patent on diagnostics methods," says Conley. "The Supreme Court seemed to say that most correlations doctors rely upon are laws of nature and acting in an obvious way in response to a correlation is not actionable. . . . The Supreme Court found the method so simple, primitive, and obvious."

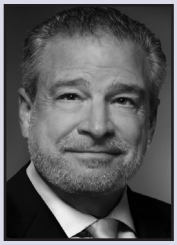
But most patent cases end at the Federal Circuit, and its recent rulings have been fractured.

"The Federal Circuit is a complete mess right now with respect to methods. They twice allowed Mayo to go through and the Supreme Court saw it as blindingly obvious. . . . There will be a market impact if the Federal Circuit cannot agree on standards for methods patents."

Given the increasing reliance on bioinformatics for interpretation of genomic data, Conley notes that the Federal Circuit's decision in *CLS Bank Int'l v. Alice Corporation Pty Ltd*. regarding software patents could impact the diagnostics industry. The court ruled that the method and computer-readable medium claims of four patents were not patent-eligible as they covered an "abstract idea." The panel stated that "adding generic computer functions to facilitate performance provides no substantial limitation and therefore is not 'enough' to satisfy section 101." Court observers note that while seven of 10 participating judges rejected the patents, there was no majority opinion. With five different opinions rendered in the case there was little clear guidance on what functions should be considered "generic" and what functions would add enough technical substance to substantiate a claim.

G2 INTELLIGENCE
Inside the Diagnostics Industry

Caris Life Sciences Expanding Molecular Profiling To Help Guide Therapy Selection



David D. Halbert, Chairman and CEO, Caris Life Sciences

Caris Life Sciences (Dallas) is an oncology-focused reference laboratory that offers more than 70 clinically relevant molecular profiling tests to help guide therapy selection for ordering physicians. The Caris Molecular Intelligence (CMI) profiling service correlates molecular data generated from a patient's tumor with biomarker-drug associations cultivated from the clinical cancer literature and worldwide databases. Testing is performed in the company's CLIA-certified laboratory, which maintains a technology-agnostic approach to tumor profiling. Of the 50,000 patients profiled to date, the company has employed mutational analysis with Sanger sequencing, next-generation sequencing (NGS), polymerase chain reaction and fluorescent in situ hybridization/chromogenic in situ hybridization, as well as methylation analysis and protein expression by immunohistochemistry studies.

Following the $725 million divestiture of its anatomic pathology practice in 2011 to Miraca Holdings, a Japanese clinical laboratory service provider, Caris became exclusively focused on molecular diagnostics and theranostics for cancer. *DTTR* recently spoke with David D. Halbert, Caris's chairman and CEO, regarding the future of clinical molecular profiling as well as the challenges the molecular diagnostics industry must overcome to realize the full clinical value of molecular oncology information.

What is driving the growth at Caris and what testing in the pipeline will contribute to future growth?

At Caris, we have two distinct offerings—our Molecular Intelligence tumor profiling service and our proprietary blood-based diagnostic platform we call Carisome, which we plan to launch later this year for the diagnosis of cancer.

Regarding our molecular profiling service, we are a reference lab, so we run whatever markers the ordering physician requests. We test only markers that are clinically relevant using whatever technology is indicated by the scientific evidence. Our service is most useful for rare and refractory cancers—the patients for whom really there are no treatment alternatives and additional clinical guidance is desired. We typically run a broad spectrum of clinically relevant markers. We have an evidence team, a group of five to six Ph.D.s and M.D.s, who read the literature worldwide and make recommendations scoring the evidence to aid the physician when choosing a therapeutic regimen. We find many oncologists have limited experience with molecular profiling. We do the best job we can to educate them on the level of evidence that is out for each marker and correlation to a particular drug in a particular lineage. Caris is a service provider and educator of oncologists.

We also have a proprietary blood-based diagnostic platform, Carisome, which is planned for launch later this year for the diagnosis of cancer. We figured out a way to isolate circulating microvesicles from blood and interrogate them in a way that

can determine the presence of cancer. Carisome assays for early diagnosis of prostate and breast cancers are planned for launch later this year. It will be marketed to high-risk populations—urology practices for men who are trying to determine if they need biopsy with elevated PSA, and for women, it will be targeted to those patients with dense breasts.

What is driving penetration of molecular profiling in clinical oncology and what challenges must be overcome to realize its full potential?

While molecular profiling has been adopted as part of the community standard of care as evidenced by the number of FDA-approved companion diagnostic tests now in use, part of the problem we face in driving market penetration is that, in many cases, formal medical education did not historically include enough emphasis on molecular biology, or even general biology, which has led some physicians to misunderstand or have misconceptions of what molecular profiling can offer. This knowledge void only widens once the student becomes a practicing oncologist, who sees 30 patients a day and simply doesn't have the time to read the enormous amount of biomarker literature that emerges daily. Our service not only vets and scores this data for them, but gives the oncologist actionable drug correlations they can use to determine a treatment path forward.

Caris has recently announced expansion of its NGS services. How does the company decide which markers to test for using NGS?

We found some of our customers were curious about markers where there was really no evidence to support clinical relevance today. But for research purposes they are interested in seeing if there are correlations that might benefit future patients, if not today's patient. But our primary offering is really based on helping patients today. We include only clinically relevant markers on the panel where there is evidence to support the correlation for or against clinical utilization of a particular medication or treatment. In our future next-generation sequencing offering, we plan to expand to over 400 genes. To come up with this number, we looked at relevant databases to find any markers that had ever been associated with cancer.

Caris Life Sciences 'By-the-Numbers'

- 342 employees across the United States and Europe
- 66,000 square-foot CLIA laboratory in Phoenix (also New York state-approved)
- 14,600 tests performed in 2012
- 80 molecular assays in use for both Caris Molecular Intelligence and Carisome
- 16 worldwide patents received and more than 100 pending
- 50-plus scientific communications published or submitted related to both Caris Molecular Intelligence and Carisome

How does the company deal with the ethical issues such as incidental findings and recontacting patients as new variants become known?

An incident occurred a few weeks ago where a new variant had become known. We went back and looked at all of our patients. It just affected five patients and we called each of those physicians to let it be known. I don't know that we can do all patients

forever for every variant, but right now that is what we are doing. We have geneticists full-time on staff constantly evaluating variants as well as our evidence team.

Coverage and reimbursement have been thorny issues this year with the transition to new MoPath codes. How does the industry need to address this transition period and how do you see coverage and reimbursement issues playing out over the next few years?

Reimbursement is abysmal. To this end, we remain very active in Washington, with full-time staff that is responsible for engaging Congress and CMS and others. Unlike drug reimbursement, there is no free market mechanism for setting pricing and reimbursement standards. We are putting together coalitions with other lab companies to stop these horribly irresponsible levels of reimbursement and coverage, which are arbitrarily set, inconsistently applied, and developed in a completely nontransparent way. I believe in America and in the long run, I have to believe that citizens won't sit by idly and let the American health care system deny profoundly sick people access to this critically important technology.

In the eyes of policymakers, many molecular tests fail to demonstrate clinical utility. How should labs and test developers best address this deficit to ensure molecular tests are evaluated fairly?

The medical community is used to seeing double-blinded clinical trials for drugs, but there is no economic rationale to support that type of model for diagnostics. The only trials you are going to see on markers are those that are funded by either pharmaceutical companies or governmental entities.

While this is the case for traditional clinical trials, we do our own research through the Caris Registry. In the registry, we have patients that we profile and track longitudinally and we hope to use this data to beef up the evidence. We have 50,000 patients in our database, which allows us to see, for example, what percent have HER2-positive colorectal cancer, and to track what drugs have been tried. All of this is done out of our pocket. We have invested $180 million into our molecular profiling offering and have never achieved profitability, all because we want to help cancer patients. G2

Analysis From the Caris Molecular Intelligence Database

Caris presented analysis of the molecular profiling results found in its Molecular Intelligence database at the American Society of Clinical Oncology's annual meeting (Chicago; May 31-June 4). The analysis was conducted on samples from nearly 42,000 patient tumors representing more than 150 histological subtypes received from 6,400 physicians worldwide. Thirty-five percent of the cases studied (n = 14,700) were categorized as rare tumors with each of the 10 rare types assessed each having a minimum of 100 reported cases. Other tumor types studied included the 10 most common cancer types in both men and women (more than 6,000 ovarian cancers, 5,000 breast cancers, 6,000 non-small-cell lung cancers [NSCLC], 5,000 colorectal cancers, and 2,000 pancreatic cancers).

As might have been expected, well-established driver mutations and protein expression in common cancers were all identified at anticipated frequencies—such as HER2 amplification in breast, PIK3CA mutations in ER+ breast cancer, and EGFR mutations in NSCLC. However, Caris's analysis revealed unexpected novel and potentially actionable targets in both common and rare cancers. Nearly 7 percent of HER2 amplifications were in NSCLC cases and 1.6 percent of KRAS mutations occurred in prostatic adenocarcinoma. Additionally, in rare cancers, 8.3 percent of ALK alterations were in soft tissue sarcomas (STS), 10.5 percent of c-MET and 26.4 percent of EGFR gene amplifications were in melanomas, 16.3 percent of KRAS mutations occurred in cholangiocarcinomas, and 10 percent of AR expression was in STS and in cancers of unknown primary site.

"To date, Caris has profiled nearly 50,000 patients, which is the largest and most comprehensive collection of biomarker profiles in the industry today," said Zoran Gatalica, M.D., D.Sc., executive medical director at Caris and lead researcher of the study. "This study provided critical insights into the distribution of common and rare genetic and protein alterations, with direct and potential treatment implications."

Physician Education Key to MDx Adoption

Genomic markers constitute the underpinning of personalized medicine, but the realization of truly personalized medicine requires clinical application of these markers to routine care. This new paradigm of clinical practice is inherently dependent upon physician acceptance and utilization of molecular tests. Test developers and molecular diagnostic laboratories are increasingly focused on the education needed to inform providers how best to use, when to appropriately order, and how to interpret these increasingly complex tests.

Physician education emerged as a novel, yet prevalent, theme at G2 Intelligence's MDx Next conference (Las Vegas; June 12-14). This theme reflects a maturation in molecular diagnostics away from a focus on the technical capabilities of the tests and toward a focus on adoption and inherently a demonstration of molecular tests' clinical utility.

Physicians face a dizzying array of molecular tests for screening, diagnosis, prognosis, and treatment selection. Aside from the challenge of keeping abreast of the overwhelming volume of literature of emerging genomic associations, physicians may be ill-prepared in their training to absorb this information and apply genomic medicine into their clinical practice.

"For most genetic testing we must realize how little physicians know," said Nathanial Robin, M.D., a professor of genetics at the University of Alabama at Birmingham, speaking at MDx Next. "Look at physicians in their 40s and their 50s. Even at great medical schools not one word about molecular genetics was mentioned. They are not prepared for this new era of medicine."

The volume of commercially available tests is expected to increase and permeate all medical specialties in the coming years, and such tests are often available and marketed in advance of acceptance into practice guidelines, leaving physicians often at a loss—with some willing to try tests that may not ultimately be clinically appropriate and others paralyzed by lack of knowledge refusing to order any molecular tests. This lack of familiarity with genomics as a whole, and individual tests specifically, reveals a dichotomy that laboratories and test developers must address—some physicians have unrealistic expectations for what genomics can and will achieve, while others undervalue the usefulness of genomics in medicine. It is increasingly incumbent upon laboratories and molecular test developers to address physicians' dearth of genomic knowledge in order to drive adoption of their molecular tests.

"Look at physicians in their 40s and their 50s. Even at great medical schools not one word about molecular genetics was mentioned. They are not prepared for this new era of medicine."
—Nathanial Robin, M.D.

"Genetic testing is another level of resolution," explained Robin. "An X-ray was better than a physician's exam and an EKG was better than a physician's exam. Genetic testing tells us something we wouldn't know otherwise, but we can't overdramatize it. It is the same as any other medical test. We need to support clinicians to understand increasingly complex laboratory results and we need to explain the limitations of these tests."

The Knowledge Gap

"Here's the snapshot—clinicians are trying to use this technology and they're desperately in need of some background, learning, and teaching about how to do this," said Jeffrey Weitzel, M.D., director of clinical cancer genetics at City of

Hope (Duarte, Calif.) and author of a recent study on physicians' attitudes toward adoption of molecular tests. "We're very rapidly being thrust into having these tools but not really knowing how to use them effectively."

Researchers from pharmacy benefit manager Medco Health Solutions (now Express Scripts) conducted an anonymous, fax-based survey of a nationally representative sample of 10,303 participating physicians. The study sought to establish a benchmark measure of U.S. physicians' level of knowledge and current use of pharmacogenomic testing. Among the findings, published in *Clinical Pharmacology & Therapeutics* in March 2012, the researchers found that 97.6 percent of responding physicians agreed that genetic variations may influence drug response, but only 10.3 percent felt adequately informed about pharmacogenomic testing. Less than one-third (29 percent) of physicians overall had received any education in pharmacogenomics. As a result, only a minority—2.9 percent of physicians—had ordered a test in the previous six months and only 26.4 percent anticipated ordering one in the next six months.

"Our findings highlight the need for more effective physician education on the clinical value, availability, and interpretation of pharmacogenomic tests," write the authors, led by Eric Stanek, Pharm.D., then from the Medco Research Institute.

The Medco study dealt with relatively straightforward testing of known drug-related genetic variants. Weitzel's study went a step further, surveying community-practicing physician members of a nationwide clinical cancer genetics network. While it is assumed that those practicing in this area may inherently be more familiar with single-gene genetic cancer risk assessment (GCRA), the study explored the clinicians' willingness to order more sophisticated multigene or whole-exome/genome sequencing. Generally, the more complex the test the less confident the physicians were in their ability to interpret and counsel about the test.

The study, presented at the annual meeting of the American Society of Clinical Oncology (Chicago; May 31-June 4), found that of the 94 physicians responding to the online survey, 27 percent ordered at least one multigene panel for genetic cancer risk assessment and only about 2 percent of the physicians ordered whole-genome or -exome tests. Among the top reasons cited of why respondents did not order multigene or whole-genome tests included concerns about how useful they would be in a clinical setting, the challenge of interpreting and communicating results, lack of knowledge about them, and the potential costs of these broader tests.

The authors concluded that the "findings suggest that while NGS tests are entering the realm of GCRA, multidisciplinary genomics education and clinical support resources are needed to address barriers to utilization and promote successful integration of NGS testing into community-based GCRA practice settings."

Physicians Are Willing to Learn

While it is increasingly recognized that physicians do not have the genetic knowledge base to incorporate widespread molecular testing into their current practice, there is some good news. Physicians are willing to learn.

Physicians face an "interest-information gap" with respect to molecular testing, according to a study conducted by health care communications agency CAHG (an Omnicon Group), with physicians' interest in molecular testing outpacing their knowledge of genomics.

CAHG conducted a Web-based survey of 801 physicians (released July 2011) to gauge awareness, adoption, and attitudes in the practice areas of oncology, cardiology, and primary care. These specialties were chosen as having likely high, middle, and low penetration and awareness of molecular tests. Surveyed physicians had been primarily in office-based practice for between two years and 35 years and were geographically evenly distributed. For analysis the total number of physicians was weighted to reflect the U.S. population of physicians across the three specialties.

The survey's key finding was that a gap exists with physicians acknowledging the growing influence of genomics-based medicine but admitting their own personal limited knowledge of the subject. Only about 20 percent of physicians received personalized medicine education in medical school, and even among those who graduated within the past five years, less than half have received such training. Cardiologists and primary care physicians express very low confidence in using molecular diagnostics in their own practices. But the physicians express that they are eager to learn more. CAHG concludes the diagnostics industry can provide significant value to an emerging critical potential customer base through information and education.

CAHG Study 'By-the-Numbers'

The specific insights gained from the CAHG physician survey include:

- 87 percent of physicians believe genomics-based medicine will have "some" or "great" influence on the medical profession.
- 41 percent say they are "not very" or "not at all" familiar with current issues and advances in genomics-based medicine.
- 50 percent report not receiving genomics-based medicine education or training either in medical school or post-medical school. (As might be expected, oncologists [71 percent] reported having received significantly more post-medical school education in genomics-based medicine.)
- 35 percent of primary care physicians (PCPs) and 50 percent of cardiologists feel "somewhat" or "completely" confident in their ability to *choose* the right test.
- 42 percent of PCPs and 52 percent of cardiologists are "somewhat" or "completely" confident in their ability to *interpret* test results.
- 45 percent of PCP and 57 percent of cardiologists felt "somewhat" or "completely" confident in *identifying appropriate* patients for testing.
- 37 percent of physicians said they would use a molecular diagnostic to *screen* a presymptomatic patient for a condition or disease with no treatment option and 41 percent would use such a test to diagnose a patient even in the absence of a treatment option.
- 30 percent of PCP, 35 percent of cardiologists, and 56 percent of oncologists are "somewhat" or "completely" confident in knowing which laboratory to send tests to.
- 93 percent of physicians report being "somewhat" or "very" interested in learning more about how genomics-based medicine relates to their practice.

"The prescription for adoption may be a dose of education," said Jeremy Coamey, practice leader of personalized medicine at CAHG, in a statement. "The significant need for education emerging from our study also provides significant opportunity for developers and marketers of molecular diagnostic products and services (as well as pharmaceutical and biotech companies developing potential companion therapeutics) to gain access, cultivate relationships, and provide ongoing value to end users of their products and services. What is particularly encouraging is the strong interest from physicians in gaining more knowledge and in meeting with sales representatives."

Strategies for Education

Experts agree on two general strategies for improving provider understanding of molecular tests. First, for successful utilization, genetic literacy must be improved for physicians and other health providers—both through increased exposure in formal curriculum and in post-formal training in continuing education. Adoption would also be improved if the general public had a basic level of genetic knowledge. Second, laboratories and test developers must step up in these education efforts by providing end-user education about molecular diagnostic products and services.

"We can't expect the average physician to explain results. Labs must provide support," said Robin. "A report must include the findings and the significance with references. They expect labs to give that kind of support to help clinicians understand increasingly complex results. A report without appropriate explanations is a disservice to the patient. The main point is to say, 'We're available.' Partner with clinical geneticists to educate physicians."

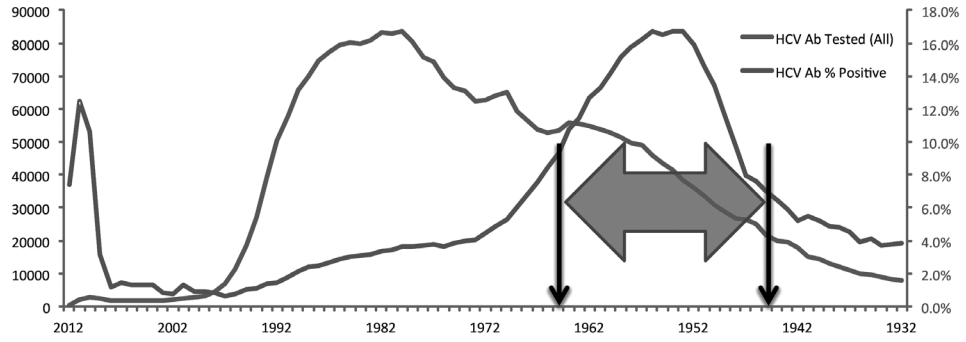
Laboratories must maintain a relationship with individual clinicians and help educate them individually, according to their preferences. Blasters of new molecular offerings will not convert physicians to be users of genetic tests, experts say.

"Mass advertising is not going to change behavior," said Theo McCormick, director business intelligence, Boston Heart Diagnostics, speaking at MDx Next. He says that with the adoption of electronic medical record (EMR) systems and enhanced practice-management tools, aggregated data can be a powerful educator enabling comparisons of testing at the physician, practice, network, and community levels. "With visualization of their patients versus a colleagues', a clinician can realize they have a problem. Labs and EMRs can provoke that realization. . . . It's these comparisons that can lead to insights that improve care."

Learning From Tests Not Achieving Widespread Adoption

In focusing on how to best educate physicians about molecular testing, speakers at MDx Next suggested the need to take some lessons from cases where testing has not been as successfully adopted as hoped, as was the case of single-gene pharmacogenomic tests, like those testing for the CYP450 variant.

"Physicians scratched their heads and didn't know what to do with it," said Dietrich Stephan, Ph.D., CEO of SV Bio. Citing reimbursement challenges and disruptions to physician workflow he says it just caused too much friction to be widely adopted. "Diagnosticians who consume the information have to make sense of it," Stephan says and this is a particularly important lesson as even more complex tests like exome sequencing come down the clinical pipeline.



Source: Theo McCormick, Management Science Associates Inc.

While hepatitis C virus antibody test is not a molecular test, McCormick cites it as an example of how aggregated visual data can play a crucial role in influencing test adoption. Management Science Associates (Pittsburgh), a provider of information management and data analytical services, reviewed 3,053,120 deidentified HCV antibody test orders and results. While this real-world data supports the U.S. Centers for Disease Control and Prevention updated testing guidelines to include universal, one-time hepatitis C testing among all persons born between 1945 and 1965, such a graphic can powerfully educate providers on the need to improve testing adherence.

COPD Exacerbation May Be Predicted With Inflammatory Markers

In patients with stable chronic obstructive pulmonary disease (COPD), elevated levels of a combination of three inflammatory biomarkers may predict an increased risk of having serious exacerbations. According to a study published in the June 12 issue of the *Journal of the American Medical Association*, simultaneously elevated levels of C-reactive protein (CRP), fibrinogen, and leukocyte counts were tied to an increased risk of having exacerbations, even in those with milder COPD and in those without a history of previous exacerbations.

Currently, the best predictor of exacerbations in all grades of COPD is a previous exacerbation; however this method has a low positive predictive value. Previous studies have found that elevated levels of inflammatory biomarkers like CRP (cutoff 3mg/L), fibrinogen (cutoff 14 μmol/L), and leukocytes (9 X109/L) during stable COPD are associated with poor outcomes and in this study the researchers sought to determine if there was also an association with exacerbations.

The researchers examined a subcohort of 6,574 patients with COPD participating in two general population studies—the Copenhagen City Heart Study (2001-2003) and the Copenhagen General Population Study (2003-2008). The subset of COPD patients did not have self-reported asthma. Baseline biomarker levels were measured in participants when they were not experiencing symptoms of exacerbations. Exacerbations were defined as short-course treatment with oral corticosteroids alone or in combination with an antibiotic or as a hospital admission due to COPD.

Over a median of four years of follow-up there were 3,083 exacerbations recorded (mean, 0.5 per participant) with 931 individuals having at least one exacerbation and 423 having frequent exacerbations (two or more less than one year apart). Risk of having at least one exacerbation and risk of having frequent exacerbations increased stepwise with the number of high inflammatory biomarkers. In the first year of follow-up, when adjusting for other variables, the odds for having frequent exacerbations increased significantly from 17 events per 1,000 person-years for individuals with one high biomarker to 32 events per 1,000 person-years for individuals with two high biomarkers to 81 events per 1,000 person-years for individuals with three high biomarkers compared with individuals who had no elevated biomarkers (nine events per 1,000 person-years).

"Our study provides novel information that may lead to a simpler assessment using measurements of inflammatory biomarkers in individuals with stable COPD to further stratify preventive therapies based on absolute risk of frequent exacerbations," write the authors, led by Mette Thomsen, M.D., from Copenhagen University Hospital in Denmark.

Addition of New Markers May Improve RA Diagnosis

Four new biomarkers have been identified that can help in the early diagnosis of rheumatoid arthritis (RA), according to a study presented at the annual meeting of the European League Against Rheumatism (Madrid; June 12-15). The findings may improve RA diagnosis, particularly among the one-third of patients who test negative for current diagnostic markers–rheumatoid factor (RF) and antibodies directed against cyclic citrullinated peptides (ACCP).

The researchers utilized enzyme-linked immunosorbent assay antibody reactivity testing to assess four candidate biomarkers (UH-RA.1, UH-RA.9, UH-RA.14, and UH-RA.21) in 127 RA patients, 97 healthy controls, and 87 patients with other rheumatic conditions. Additional testing was performed in a validation cohort of 166 RA patients. The study population included 52 early RA patients.

Of the total sample of 293 RA patients, 24 percent could not be identified using the current diagnostic biomarkers RF and ACCP. But the four candidate biomarkers identified RA in 26 percent of the RF-negative, ACCP-negative population, thereby reducing the serological gap from 24 percent to 17 percent. Of the 69 seronegative RA patients, UH-RA.1 identified 7 percent and UH-RA.21 identified 17 percent. Combining all four markers into one panel achieved a sensitivity of 30 percent and a specificity of 83 percent for RA. These biomarkers were present in early disease stages, with 37 percent of the early RA patients testing positive—12 percent were positive for UH-RA.1 and 27 percent were positive for UH-RA.21.

"The detection of antibody reactivity against our candidate biomarkers in 37 percent of early and 26 percent of seronegative RA patients implies that these biomarkers can be of additional value to the current diagnostic biomarkers for RA, with most promising results for UH-RA.1 and UH-RA.21," wrote lead author Liesbeth M. De Winter, a Ph.D. student at Hasselt University in Belgium. "Significant associations with inflammatory factors and disease activity indicate an important prognostic potential as well."

First Trimester Marker May Predict Gestational Diabetes Risk

Increased soluble (pro)renin receptor (s(P)RR) concentrations during the first trimester may predict the development of gestational diabetes mellitus (GDM) later in pregnancy, according to a study published in the June issue of the *Journal of Clinical Endocrinology & Metabolism*. With further validation, particularly in more diverse populations, s(P)RR holds the potential for filling a clinical gap in the screening of GDM early in pregnancy.

With current screening methods, low-risk women with the potential to develop GDM are typically not identified until late second trimester, when low-risk women undergo a 50 gram, one-hour loading test, the glucose challenge test (GCT) at 24 weeks to 28 weeks of gestation. By contrast, in this study, women in the highest s(P)RR concentration quartile (over 34.2 ng/mL) during the first trimester were 2.90-fold more likely to develop GDM than women in the lowest quartile (less than 25.8 ng/ML). s(P)RR is a marker of activation of the tissue renin-angiotensin system, which is tied to adverse complications in patients with diabetes and hypertension.

The researchers conducted a prospective study of 716 pregnant Japanese women who first visited a referral birth center at a tertiary hospital at less than 14 weeks of gestation between 2010 and 2011. A random blood glucose test (random time, regardless of the timing of the subject's last meal) was administered during the first trimester (less than 14 weeks of gestation), while the 50 gram GCT was administered at 24 weeks to 28 weeks of gestation to determine candidates to undergo the 75 gram oral glucose tolerance test.

The researchers found that 44 participants (6.1 percent) had GDM. Only one woman was diagnosed with GDM from a random blood glucose test during the first trimester, with the remaining 43 women diagnosed after the GCT. Mean s(P)RR of the entire cohort was 30.6 ng/mL and was significantly higher in women with GDM than in women

without GDM (35.5 ng/mL versus 30.3 ng/mL). The association between plasma s(P)RR concentrations and the onset of GDM was independent of GDM risk factors including baseline characteristics, medical complications, or gestational characteristics. Random blood glucose results did not differ significantly between women with and without GDM.

"Additional studies involving combinations with other risk factors and biomarkers, such as C-reactive protein, are warranted and may further improve the predictive ability of s(P)RR concentrations for GDM during early pregnancy," write the authors, led by Noriyoshi Watanabe, from Tokyo Women's Medical University (Japan).

MDx Market to Reach $7.8 Billion in 2013, G2 Intelligence Estimates

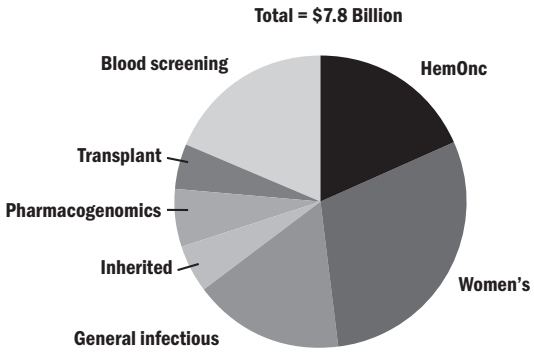
A new research report from G2 Intelligence estimates the U.S. molecular diagnostics market will total about $7.8 billion in 2013. While demand for molecular testing is expected to increase, driven by declining costs and growing acceptance of the tests in clinical practice, this growth will likely be offset by the implementation of the new molecular pathology Current Procedural Terminology codes, which will impede growth both through lower reimbursement rates as well as decreases in positive coverage decisions by payers.

G2 Intelligence used a proprietary market-sizing methodology that integrates different estimation approaches through a "triangulation" of data from diverse sources, including surveys of laboratories, modeling of disease incidence and testing guidelines, secondary market research, and top-down estimates from Medicare resources. Market size estimates, growth rates, and MDx market subsegments were all calculated using this methodology.

The seven market subsegments include hematology, women's health, general infectious disease, inherited genetic diseases, pharmacogenomics, transplant, and blood screening. MDx is defined in the report as including nucleic acid assays utilizing polymerase chain reaction, in situ hybridization, sequencing, microarrays, cytogenetics, electrophoresis, and genomic immunohistochemistry techniques.

Though molecular diagnostics represents a small share of the total clinical laboratory testing market, it is the fastest-growing segment. While hospital or academic university laboratories made up the majority of the laboratories offering clinical MDx testing in 2012 (70 percent), independent laboratories (including reference or specialty laboratories) had the majority of the MDx test volume in 2013 (62 percent).

MDx 2013 Midpoint Market Sector Estimates



Source: G2 Intelligence, *U.S. Molecular Diagnostic and Genomic Testing 2013-2015: Laboratory Industry Analysis, Trends, and Forecasts*

G2 Intelligence's new report, "U.S. Molecular Diagnostic and Genomic Testing," provides detailed analysis of the entire molecular market, major molecular diagnostic sectors, the dynamics of molecular reimbursement, and lab-developed tests. The report also includes overall market size and projections for each sector through 2015, analysis of key market drivers and inhibitors, and platform usage analysis by test type.

The report is available for purchase for $1,195 at *www.G2Intelligence.com*. For multiuser or multilocation pricing, contact Jonathan Wentworth-Ping at 603-357-8160 or *jping@G2Intelligence.com*.

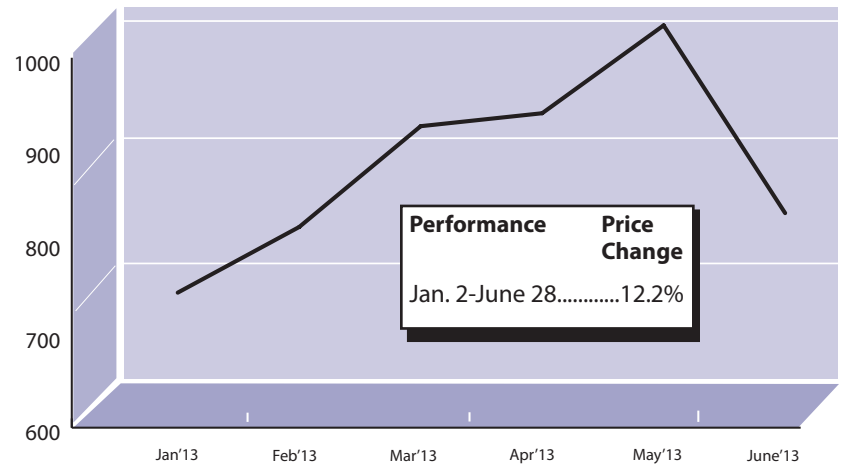
G2 Index Up 12% So Far in 2013, Surpasses Broader Market

The G2 Diagnostic Stock Index gained 12 percent during the first half of 2013 (Jan. 2 to June 28). Twelve stocks gained for the period, while three stocks lost ground. The G2 Diagnostic Stock Index outperformed the broader stock markets for the first half of the year. The Nasdaq and the S&P 500 both gained markedly over the same period, with the Nasdaq up 9 percent and the S&P increasing 10 percent. While the gains were widespread, eight of the 12 stocks that were up for the period had gains in excess of 20 percent. These large gains were shared by both large and small companies.

The stock gaining the most so far this year was **Illumina** (San Diego). In May, Illumina announced the launch of its BaseSpace cloud computing and storage platform and an associated bioinformatics app store. Among the first commercially available apps was scientific publisher Elsevier's Genomics Data app, which allows researchers to share large data sets in Illumina's BaseSpace cloud for easy review and inclusion in Elsevier's open access journal, *Genomics Data*. While BaseSpace is not expected to significantly contribute to Illumina revenues in the short term, it may increase business leads and ultimately contribute to profits. So far for the year, Illumina's shares gained 35 percent, jumping from $55.42 in early January to $74.84 at the end of June, driven both by the company's continued market dominance and on speculation that it remains a takeover target.

OraSure Technologies (Bethlehem, Pa.) ended the first half of the year down the most in the index: -46 percent. Despite the company's continued optimism for its In-Home HIV Test, its rapid hepatitis C test, and its molecular collection system by its subsidiary DNA Genotek (DNAG), profits were down for the first quarter of 2013 with net losses increasing to $10.2 million, compared to a net loss of $3.3 million for the first quarter of 2012. At its May annual shareholder meeting, CEO Douglas Michels said In-Home HIV "product sales are building with promotion." First quarter had $1.5 million in gross sales of the In-Home HIV test and a 19 percent increase in net revenues from DNAG to $3.9 million. The company's net loss for the first quarter of 2013 included $6.9 million in advertising and promotional expenses for the In-Home HIV test.

G2 Diagnostic Stock Index



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

Up	Price	% Chg
Abaxis	47.51	26%
Abbott Labs	34.88	10
Affymetrix	4.44	35
Alere	24.50	29
Becton Dickinson	98.83	26
Bio-Rad	112.20	4
Illumina	74.84	35
Johnson & Johnson	85.86	23
Luminex	20.61	20
Meridian	21.50	5
Qiagen	19.91	6
Quidel	25.53	28
Down		
Cepheid	34.42	-3%
OraSure	3.88	-46
Sequenom	4.21	-15

G2 Insider

Urine Screening Alone Significantly Underestimates STIs. . . A study of high-risk, gay men found that urine screening alone misses a significant number of sexually transmitted infections, according to an abstract presented at the annual meeting of the Pediatric Academic Societies (Washington, D.C.; May 4-7). Non-genital chlamydia and gonorrhea (CT/GC) infections may contribute to the burden of infections in this high-risk population and might be missed by a genital (urine screen). A strategy employing triple screening (urine, throat, and rectum samples) may greatly enhance detection of infected individuals.

The U.S. Centers for Disease Control and Prevention recommends routine laboratory screening for common sexually transmitted diseases for all sexually active men who have sex with men, with test selection based on types of reported intercourse. However, detailed, accurate sexual histories of youth are not always taken, especially in primary care settings.

The researchers analyzed clinical information and GC/CT nucleic acid amplification tests on urine, pharyngeal, and rectal specimens from a young, urban population of 118 men who have sex with men (aged 14 years to 24 years) presenting for care at a community-based, high-risk youth center between March 1 and Oct. 30, 2012. Thirty-six screened patients were positive at one or more sites for gonorrhea, chlamydia, or both. CT was detected in urine, rectal, and pharyngeal samples in two, 11, and two cases respectively, whereas GC was detected in urine, rectal, and pharyngeal samples in nine, 18, and 18 cases respectively. Relying exclusively on urine testing alone would have missed 86 percent of CT infections and 70 percent of GC infections. Rectal testing alone missed 21 percent of CT infections and 38 percent of GC infections, while pharyngeal testing alone missed 78 percent of CT infection and 38 percent of GC infections.

"Notably, rectal screening appeared to have the highest yield, significantly more than urine screening," write the authors, led by Faiza Ali, M.D., a pediatric infectious disease fellow at Washington University in St. Louis. "Further studies are needed to determine disease prevalence and best screening strategies in other high risks youth groups such as HIV+ adolescents."

Company References

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