G2 INTELLIGENCE
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Diagnostic Testing & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

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Cold Spring Harbor Laboratory to Expand Quantitative Biology

Cold Spring Harbor Laboratory (CSHL; Cold Spring Harbor, N.Y.) announced a $50 million gift to establish a center for quantitative biology. The Center's establishment is part of a trend in which both research and clinical laboratories are investing heavily in bioinformatic analysis capabilities.

The Simons Center for Quantitative Biology, established with a $50 million gift from Jim Simons' foundation (he applied mathematical expertise to financial markets), will bring together experts in applied mathematics, computer science, theoretical physics, and engineering to further basic research and investigation into illnesses including cancer, autism, bipolar disorder and depression.

"The pace of modern science and the vast amount of data being generated, both in genomics and imaging, has necessitated an expansion of our research to include scientists with expertise in quantitative analysis" said Bruce Stillman, CEO of CSHL, in a statement. For more information on trends in interpretation of next-generation sequencing results, please see *Inside the Diagnostics Industry* on page 5.

G2 Predicts Majority of CLIA Labs Doing Cancer Testing Will Use NGS Within 5 Years

In the coming three to five years, more than half of U.S. CLIA laboratories that perform tumor testing will begin to offer next-generation sequencing (NGS)-based services, according to G2's recently released report *Clinical Next-Gen Tumor Sequencing: Your Key to the Value-Driven Oncology Market*.

The report, based on qualitative interviews with NGS stakeholders, including hospital and independent laboratories as well as sequencing platform and service vendors, assesses the current state and anticipated evolution of NGS within oncological practice, the current leading clinical area of NGS testing.

While the industry marvels at the speed with which the cost of sequencing has plummeted, NGS has for all practical purposes not truly reached the awaited $1,000 per genome threshold. Yet adoption of NGS-based testing is permeating clinical care at a pace unlike any other technology seen in the modern era of laboratory medicine. Clinical NGS testing is currently available for evaluation

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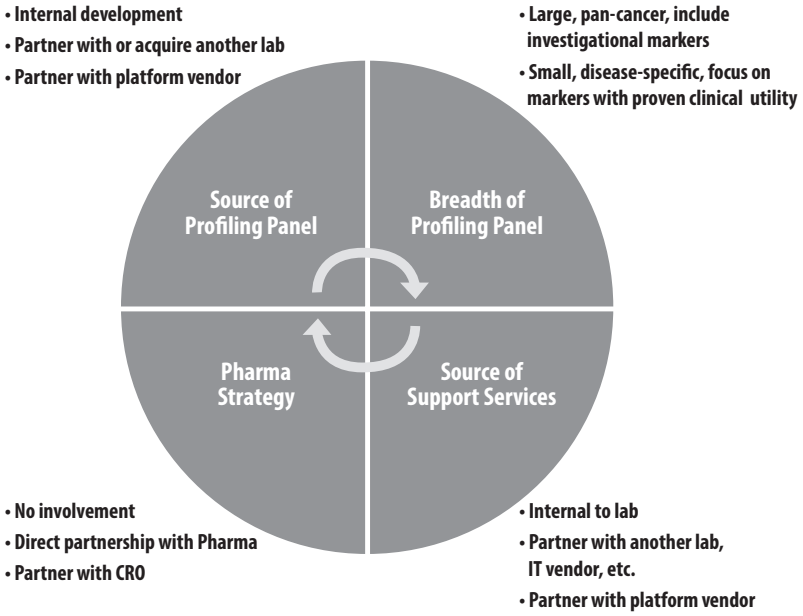
▲ **Growth of NGS Testing in CLIA Labs,** *from page 1*

of somatic mutations in both solid tumors (lung, breast, prostate, or colon) and liquid malignicies (lymphomas, leukemias), although the report finds that the most rapid adoption of NGS testing has been seen in lung cancer care, largely because of the availability of targeted therapies. Only a fraction of the NGS market is for hereditary cancer targeting germline mutations.

Early NGS adopters include academic medical center laboratories, large reference laboratories, and specialty laboratories. However, adoption of NGS testing by smaller labs is anticipated in the coming years, driven by community-based oncologists. For labs that are early adopters, the report finds that there are three dominant market opportunities: partnering with pharmaceutical companies or contract research organizations in support of clinical trials or biomarker development, direct commercial clinical testing, and commercializing and licensing NGS panels or support services (bioinformatics and interpretation services).

Landscape of Approaches to NGS



Source: G2 Intelligence. *Clinical Next-Gen Tumor Sequencing: Your Key to the Value-Driven Oncology*

Of course to realize the market opportunities, several challenges must be overcome, including clinically meaningful interpretation of results. Downstream implications of the interpretation challenge are immature NGS guidelines and difficulty generating evidence of clinical utility, which in turn impact regulatory approval and reimbursement.

The report says that the U.S. Food and Drug Administration's 2013 approval of Illumina's MiSeqDx sequencing platform "may serve as a green light to laboratories looking for regulatory clarity regarding the use of NGS in clinical settings."

As with the broader molecular diagnostics reimbursement landscape, laboratories are stymied by a lack of clear-cut policies to guide payer decisions of innovative tests. The system currently lacks appropriate coding for submitting NGS claims. As codes are developed, all NGS test providers will need to work toward establishing evidence of clinical utility of NGS tests for payers. While definitive evidence is still lacking, many hold that NGS does afford a promising value proposition as it has the potential to improve the value of oncological care by streamlining the diagnostic process, reducing wasteful spending on ineffective therapies; improving clinical outcomes; and identifying end-of-life patients best served by palliative care.

To Read the Full Report

Clinical Next-Gen Tumor Sequencing: Your Key to the Value-Driven Oncology Market is available for $1,195 from G2 Intelligence *(www.G2Intelligence.com).*

Despite the ecosystem challenges, G2 predicts "accelerated" adoption over the next five years. A sharp uptick in the number of U.S. CLIA laboratories using NGS tumor testing is expected—from 7 percent in 2013 to an anticipated majority in five years. While initial focus of NGS has been on the capabilities of the technological platforms, industry interest is burgeoning in bioinformatics service vendors. These vendors will play a pivotal role in the broader transition of NGS into clinical practice, given the limited availability of resources and talent to create proprietary interpretation algorithms, particularly in smaller, community laboratories or oncology practices.

Takeaway: NGS tumor testing is expected to proliferate in the next several years as smaller laboratories adopt the technology, driving related growth among NGS service vendors including bioinformatics and interpretation providers. G2

MALDI-TOF Generates Substantial Cost Savings

Utilizing matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (MS) can yield substantial cost savings for laboratories over traditional microbiology methods, according to a study presented at the American Society for Microbiology general meeting (Boston; May 17-20). Over a single year, the researchers say that MALDI-TOF saved the microbiology laboratory 92 percent in just reagent costs alone. Although the up-front instrumentation cost is high, the cost of identifying an isolate can be very low.

University of North Carolina (UNC) Hospitals purchased the MALDI-TOF MS in 2012 for approximately $250,000. Although the laboratory tested both the Bruker and bioMérieux systems, they ultimately purchased the system from bioMérieux, which is headquartered 10 miles away.

"We found the system really revolutionary, and that is not exaggerating," Peter Gilligan, Ph.D., director of the clinical microbiology-immunology laboratories at UNC Hospitals, tells *DTET*. "The biggest advantage is that it is fast and quite accurate for 95 percent of isolates. It takes minutes to make identifications that previously took days."

In the cost-effectiveness study, 21,930 isolates were directly compared on MALDI-TOF MS and conventional methodologies from April 1, 2013, to March 31, 2014. These specimens consisted of enteric pathogens, enterococci, gram-negative nonglucose fermenters, staphylococci, streptococci, and yeast. Costs for MALDI-TOF MS were calculated two different ways: perfect identification and a "real world" identification that allowed for repeat spotting.

The researchers found that traditional identification of the nearly 22,000 isolates would have cost $84,491 in reagents alone, compared to $6,469 for MALDI-TOF MS, yielding a net savings of 92 percent in reagent costs in an ideal scenario where only one identification was required per isolate. When including the time spent by lab technologists, cost savings totaled $118,260 for one year, an 82 percent reduction.

"The cost savings are very clear for the microbiology lab. It will take two to three years to pay for the equipment from the cost savings generated," Gilligan says. "What we don't know yet is if the institution is going to receive other downstream benefits. An outcomes study is underway to examine the benefit beyond the laboratory."

The study was part of a presentation to hospital administrators justifying the purchase.

"This was the most expensive piece of equipment—by quite a bit—my laboratory ever bought. We have tremendous credibility with the hospital administration, so they believed us when we told them there would be cost savings," says Gilligan. "We have an ever-increasing workload, and the hospital wasn't going to give us more people, but it did buy us this equipment that allowed us to become more efficient."

Currently Gilligan says that his lab identifies between 80 and 100 isolates in an eight-hour shift, which can be "comfortably" increased to 350 isolates in eight hours "if workload demanded this." As information technology improvements connect microbiology laboratories throughout the UNC system, Gilligan is confident the existing MALDI-TOF system in his laboratory can handle increased volumes resulting from testing sent in from satellite facilities.

"We have a community-sized hospital 20 minutes away; would you put a mass spec system there? Absolutely not," Gilligan explains, when asked about the volume necessary to justify the expense of a MALDI-TOF system. "During the time of the study, we were doing [almost] 22,000 identifications per year and we are an 850-bed hospital. If you had 50,000 [identifications] it would pay for itself faster. Would it make sense for a 100-bed hospital? I'm not sure."

A key to making the calculation, Gilligan says, is accounting for the time frame in which the technology will become obsolete. This technology window used to be much longer than it currently is.

"With blood cultures we used the same techniques for 25 years. There were different platforms, but the same general approach. With HIV testing we are in the fourth generation in 30 years, so about a 7.5-year window. With molecular testing we are running in closer to three-year cycles," Gilligan says. "As for MALDI-TOF, for now this is the best microbiology technology there is."

However, Gilligan would advise other laboratories considering making the switch to MALDI-TOF to evaluate the financials using a three- to five-year technology window.

Takeaway: Aside from the potential clinical advantage of having a significantly shorter time to results of pathogen identification, evidence is emerging as to the substantial cost savings and efficiency gains that employment of MALDI-TOF technology can bring to microbiology laboratories.

A Public Health Lab's Experience With MALDI-TOF

The New York State Department of Health (Albany) Wadsworth Center (WC) Bacteriology Reference Laboratory fully implemented MALDI-TOF into its workflow in 2013. The laboratory evaluated its experience during the first 11 months of MALDI-TOF. It found that:

- 1,700 clinical isolates (1,400 unique specimens) have been analyzed.
- 100 genera (more than 200 species) were identified.
- Using only direct smear analysis MALDI-TOF MS testing resulted in an acceptable bacterial identification for 76 percent of the specimens.
- An additional 15 percent of specimens required the formic acid-acetonitrile extraction, while 9 percent resulted in no reliable identification.
- Half of the final bacterial identification reports were based on MALDI-TOF MS alone, while 37 percent required additional biochemical analysis for species identification.
- Since MALDI-TOF implementation, there has been a 60 percent decrease in the number of real-time polymerase chain reaction tests and a 40 percent reduction in 16S rRNA gene sequence analysis.
- There has been a 45 percent reduction in the average turnaround time for final identification reports.

"This reduction in testing requirements has allowed the WC to better operate with a decreasing state budget, decreasing microbiology staff and has allowed more time to focus on other public health activities," writes lead author Lisa Mingle, Ph.D., in an abstract also presented at the American Society for Microbiology general meeting (Boston; May 17-20).

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Inside the Diagnostics Industry

Sequencing Continues Making Headlines, Though Panels Will Dominate in Short Term

Rapid incorporation of sequencing into clinical practice is stirring excitement in the molecular diagnostics industry, but in reality this method faces some hurdles. The emerging clinical applications of sequencing-based tests, as well as frank discussions of some of the challenges, were discussed at G2's MDx *NEXT* conference (Baltimore; June 11-13). Through the two-day conference, some dominant themes emerged.

Sequencing Grabbing Headlines

Sequencing will revolutionize the practice of molecular diagnostics, if it has not already. Yes, there are regulatory and reimbursement challenges ahead, but the technological aspects of next-generation sequencing (NGS) have largely been conquered. Now, attention is increasingly being focused on the remaining practical undertaking of making sense of the vast quantities of sequencing data. The point was repeatedly made that the biggest barrier to widespread clinical adoption of sequencing is data interpretation. There was both optimism and enthusiasm regarding the number of firms tackling the bioinformatics and analysis components of interpretation and the progress these startups are making. Expert stakeholders across the diagnostics industry highlighted the growth potential among this segment of the industry.

Roche Snaps Up Sequencing Firm

In a move meant to strengthen its diagnostics pipeline after its failed bid to buy Illumina, Roche (Switzerland) acquired U.S. gene-sequencing firm Genia Technologies (Mountain View, Calif.) for up to $350 million ($125 million paid immediately and $225 million contingent on achieving milestones). Unlike Illumina's platform, Genia relies upon nanopore technology. Genia, more specifically, relies on semiconductors to measure changes in electrical currents, capable of measuring single molecules, while its NanoTag chemistry, the company says, enables more accurate base calls than other nanopore-based platforms.

Analysts say the acquisition is an important long-term play for Roche. In addition to enhancing the strength of its diagnostics portfolio pipeline, Genia's technology can also potentially be used in development of targeted therapeutics.

The enthusiasm for all things sequencing is additionally buoyed by the seemingly daily headlines touting sequencing achievements, even in the lay media. The week of the conference, the *New England Journal of Medicine* published a case report (that was also heavily reported in lay media) of NGS making an "actionable diagnosis" of a life-threatening infection, a diagnosis that ultimately saved a 14-year-old boy's life.

The boy was put into a medically induced coma after being hospitalized for six weeks with a brain-inflaming encephalitis. A rapid bioinformatics analysis pipeline, developed by Charles Chiu, M.D., Ph.D., at the University of California, San Francisco (UCSF), called SURPI (sequence-based ultra-rapid pathogen identification) was able to streamline "genetic sleuthing" of disease pathogens, enabling rapid sequencing and simultaneous identification of all DNA in the patient samples without culturing or targeting for specific infectious disease agents, thus dramatically cutting the time between sample collection and diagnosis.

In this case it took 48 hours from cerebrospinal fluid (CSF) sample receipt to diagnosis of a Penicillin-treatable, bacterial infection. SURPI created a library of 10 million distinct DNA sequences from samples of the patient's CSF and blood, and from a control sample. Using a MiSeq DNA sequencer (Illumina) the researches discovered that 475 distinct DNA sequences among the 3 million DNA sequences

in the patient's CSF came from Leptospira bacteria. No Leptospira was detected in the patient's blood. Analysis of the DNA sequences took just 96 minutes, with SURPI providing an answer that an extensive infectious disease workup was unable to determine. Seven days after initiation of penicillin, the patient was discharged.

"Until now NGS has been regarded as too slow and laborious to be useful for routine infectious disease diagnosis," said study co-author Joseph DeRisi, Ph.D., chair of biochemistry at UCSF, in a statement. In this case, an experimental diagnostic protocol was utilized in a CLIA-certified clinical lab, but Chiu said that within a few months he expects to obtain approval to offer an NGS-based diagnostic test at the UCSF clinical microbiology laboratory for diagnosis of certain types of infectious diseases.

Besides continued development of rapid bioinformatic workflow techniques, appropriate reimbursement will foster larger demployment of NGS tests in routine clinical practice. Jorge Leon, Ph.D., president of Leomics Associates consulting firm, told the MDx *NEXT* crowd that he is hopeful reimbursement will begin in earnest for NGS tests in 2015. He predicts adoption of NGS to be the fastest-growing genomics platform for the next 10 years, a segment with potential new revenue of $3 billion to $4 billion.

Growth of NGS Panels

As industry experts continue to explore the growing applications of NGS, a healthy tension is apparent between the possibility of using whole-genome and whole-exome sequencing, which are notable for their cost efficiencies but yield excessive data of uncertain clinical significance, and single-gene analysis of targeted mutations with known clinical significance. While there have been notable success stories of the application of whole-genome and whole-exome sequencing to end diagnostic odysseys, current consensus is that NGS panels will dominate the sequencing landscape for the foreseeable future.

According to data unveiled for the first time at the conference by the genetic test marketplace NextGxDx (Nashville, Tenn.), the move toward utilization of panels, rather than single-gene analysis, is clearly under way. In the first five months of 2014, 1,085 new molecular tests were released, including 362 panels, a dramatic increase in the percentage of tests released as panels over previous years, Mark Harris, Ph.D., NextGxDx's CEO, told conference attendees.

"Payers want to see how to reduce the costs of tests currently being used and they want to reduce the redundancy of tests," said Leon of Leomics Associates. "If an NGS panel will report with the same or increased accuracy and the test has added value because of extra genes being tested, they would like to see that. But the big question is, are the added genes affecting outcomes. We need to show that in real patients."

Partnership to Expand Solid Tumor Mutation Panel

Providing further evidence for clinical interest in molecular panels, Memorial Sloan-Kettering Cancer Center (MSK; New York) and Quest Diagnostics (Madison, N.J.) announced a partnership in June to enhance Quest's OncoVantage sequencing-based panel. The first phase of the collaboration will be evident this summer with the launch of a cobranded clinical annotation report. The panel's analysis of 34 genes from solid tumor biopsy samples will be merged with MSK databases, correlating specific mutations to patients' prognosis, treatment selection, and monitoring of disease progression. This real-time data exchange, the companies say, will enable rapid translation of discoveries into clinically actionable information for cancer care.

The second phase of the collaboration will involve codevelopment of an expanded test potentially analyzing hundreds of genes. Launch of this test is anticipated in spring 2015.

Sherri J. Bale, Ph.D., managing director at GeneDx (a subsidiary of Bio-Reference Laboratories; Gaithersburg, Md.), offered some practical considerations for laboratories to consider when developing panels. For instance, she said there is still the expectation that there is 100 percent coverage of all nucleotides on panels. In reality, though, Sanger sequencing for LC/LQ regions is often required. Additionally, she cautioned that you can't add a new gene to an existing panel "on the fly." Changing a panel can take four to six months and $100,000 to revalidate. Despite some imperfections, panels, she says, are still a good approach for complex phenotypes.

Transparency, Workflow Improvements Needed

With increasing reliance on panels comes the challenge of making comparisons between tests—a particular challenge for ordering clinicians. The emphasis on transparency in molecular testing is permeating beyond just the payments realm and needs to be addressed during the test ordering process, Harris says. His company, NextGxDx, provides such a solution.

NextGxDx provides a comprehensive online marketplace for genetic testing. The number of commercially available tests for genetic diseases is increasing at a pace—50 tests per week, NextGxDx says—faster than hospitals and physicians can keep up with. Furthermore, researching and ordering these tests can be a cumbersome process, which can take hours of a physician's time. The NextGxDx tool enables clinicians to access up-to-date listings of all genetic tests from CLIA-certified laboratories, order tests online, and receive results electronically.

The company has a goal of including molecular test information from all U.S.-based CLIA-certified laboratories. The company collects test information, and cleans and standardizes testing information, making comparisons based on included variants, turnaround time, and price possible. NextGxDx streamlines this process and takes it one step further by simplifying ordering too. Harris says a typical hospital can order tests from 25 to 45 different laboratories, with only the largest laboratories' requisition forms (AmbryPort, ARUP Connect, Baylor GeneResults, LabCorp Beacon, Mayo Access, Quest Care360) integrated into electronic health record systems, thus necessitating the use of error-prone, time-consuming, handwritten forms for the rest.

"The goal of a marketplace is to create transparency. For industries ranging from air travel to electronics, online marketplaces have demonstrated the ability to improve overall product quality and customer service," the company says. "This is done by providing a way for users to easily compare important ordering-related information for all available products in one place."

NextGxDx incorporated elements from consumer goods models—PayPal with a secure checkout and payment system in fragmented markets; Amazon, which consolidates vendors to provide a comprehensive catalog; and Walmart with one-stop, low-cost shopping. NextGxDx receives a per-test transaction fee for any tests ordered through the platform. Health care providers will never have to pay to access the marketplace. The company has nearly 20,000 products in its catalog.

Takeaway: As clinical NGS permeates more practice areas, attention and enthusiasm are increasingly focusing on bioinformatics and analysis solutions.

Technology Evolving Slowly in U.S. Pertussis Testing

Oral fluid testing holds the potential to improve pertussis surveillance efforts, particularly for diagnosis of milder cases in patients who seek care later in the course of illness, according to a study published in June in *Emerging Infectious Diseases*. These patients represent a well-known gap in current surveillance efforts, which contributes to suboptimal identification of cases.

Pertussis, commonly known as whooping cough, is a nationally notifiable disease, and all cases are supposed to be reported through health departments to the U.S. Centers for Disease Control and Prevention (CDC) through the National Notifiable Diseases Surveillance System. Caused by the bacterium Bordetella pertussis, whooping cough has been classified as a rapidly re-emerging disease and has even reached epidemic status in some states like California, where 4,558 new pertussis cases have been identified in 2014 (through June 24), surpassing the total number of reported cases in 2013. Nationally the CDC reports a 24 percent increase in the number of cases this year (through mid-June) over 2013.

While the current surveillance system is useful for monitoring epidemiologic trends, limitations in laboratory diagnostics make reliance on the number of actual reported cases "problematic." Existing pertussis surveillance systems tend to underidentify less severe cases, particularly among older children and adults, in part due to testing technology constraints, which are limited in comparison to those used in Europe.

"We are currently having discussions to incorporate serology into case definitions. We haven't even considered oral fluid testing yet," Stacey Martin, an epidemiologist and CDC subject expert, tells *DTET*. "There are more than 40 serological assays, but none are FDA-cleared. If serology makes it to the case definition there must be tight parameters and standardization to international references, otherwise we won't know the accuracy of individual tests."

Despite the fact that the United States is likely years away from incorporating oral fluid testing into case definitions (Martin says serological incorporation is likely one to two years away), the CDC and other organizations are taking note of assay development and acceptance in other countries, as oral fluid has some advantages from both a public health and a patient preference and acceptability perspective.

The *Emerging Infectious Diseases* article details a national pilot study conducted (June 2007–August 2009) in the United Kingdom, where serologic testing is already widespread. The pilot tested the feasibility of noninvasive oral testing for routine follow-up of notified, nonconfirmed, clinically diagnosed pertussis cases. Researchers mailed oral fluid sampling kits either directly to the patients, their parents or guardians (the kit was suitable for use at home), or to their general practitioner.

The researchers found that 66 percent of test kits were returned with submitted samples. During the study

Current Diagnostic Methods

Current diagnostic methods used in the United States for pertussis include the following:

- Culture, the standard diagnostic test, has excellent specificity but takes up to seven days to get results back. Culture requires nasopharyngeal (NP) specimens collected during the first two weeks of cough, when viable bacteria are still present.
- Polymerase chain reaction (PCR) is the most rapid test for pertussis and has become the dominant test. While the NP specimen does not require viable bacteria, it should still ideally be collected during the first three weeks of illness. Epidemiologists and CDC experts express concern over the lack of standardized PCR assays, saying that sensitivity and specificity can vary greatly between laboratories, leading to variance in interpretation criteria for diagnosis.
- Serology, while used in 20 European countries, Japan, and Australia, can be used for confirmatory reporting purposes only by the Massachusetts state public health laboratory. The CDC and U.S. Food and Drug Administration (FDA) have also developed a serologic assay for confirming diagnosis, especially during suspected outbreaks. CDC says it is currently engaged in efforts to compare commercially available serologic tests. The advantage of serologic tests is that they are more useful for diagnosis in later phases of the disease—two to eight weeks following cough onset, when the antibody titers are at their highest.

period, 1,852 cases of pertussis were confirmed by established laboratory methods and another 591 cases (24 percent of all cases) by oral fluid testing only. Oral fluid testing increased laboratory ascertainment of pertussis by 32 percent overall, with the greatest increase (124 percent) among children aged 5 years to 9 years. Although patients over 20 years of age submitted the largest number of oral fluid samples, the highest proportion with positive results (61 percent) were seen in children aged 10 years to14 years. Cases confirmed by oral fluid testing were least likely to be hospitalized, suggesting that milder community cases were being identified by this method.

Oral Fluid Assay Specifications

The enzyme-linked immunosorbent assay was developed by Public Health England (then known as the Health Protection Agency) to detect IgG against pertussis toxin in oral fluid. The agency reports that the oral fluid assay detects seropositivity with a sensitivity of 79.7 percent and a specificity of 96.6 percent. Using oral fluid titers of greater than 70 arbitrary units (in the absence of pertussis vaccination within the previous 12 months) the assay has a positive predictive value of 76.2 percent to 93.2 percent for pertussis among children with chronic cough, assuming disease prevalence between 12 percent and 37 percent.

"Oral fluid testing is an easily administered, noninvasive surveillance tool that could further our understanding of pertussis epidemiology and thereby contribute to decisions on vaccination strategies," write the authors, led by Helen Campbell, from Public Health England in the United Kingdom. "Furthermore, underascertainment of milder infections causes bias, leading to overestimation of vaccine effectiveness."

Takeaway: International acceptance of oral fluid testing in pertussis surveillance is years ahead of U.S. criteria. Domestically, the focus is on standardization of commercially available serological assays, which will improve identification of later-stage pertussis cases, particularly in older children and adults. G2

Study Urges No Routine Histological Exam in Orthopedic Surgeries

Substantial cost savings could be achieved by eliminating the practice of routine histological examinations of knee arthroscopy tissue, according to a study published in the June issue of the *Journal of Bone and Joint Surgery*. These routine pathological examinations are of limited cost-effectiveness because of the low prevalence of findings that altered patient management. As a result, the authors suggest that gross and histological examinations should be performed only at the discretion of the orthopedic surgeon.

There are more than 1 million knee arthroscopies performed annually in the United States, making it the most common orthopedic surgical procedure performed. Pathological evaluation is commonly performed as routine practice on samples acquired during this procedure, due to a lack of exemption from accreditation guidelines (the College of American Pathologists and the Joint Commission).

In the present study, medical records were reviewed for 3,797 consecutive knee arthroscopies (partial meniscectomies and anterior cruciate ligament [ACL] reconstructions) performed by two surgeons (from 2004 to 2013). Pathology reports were reviewed to determine if the results altered patient care and the total costs of histological examination were estimated in 2012-adjusted U.S. dollars.

The researchers found that the prevalence of concordant diagnoses was 99.3 percent, the prevalence of discrepant diagnoses was 0.7 percent (n = 270), and there was one case of discordant diagnoses, which was refuted with further testing. Two patients were diagnosed with benign neoplasms. Neither diagnosis resulted in changes in care man-

agement. Across the 23 abnormal histological diagnoses, intraoperative findings were consistent with the histological diagnosis. The total cost of histological examinations was estimated to be $371,810, and the total cost of the pathology cost per discrepant diagnosis was $13,771, and the cost per discordant diagnosis was $371,810.

"We believe that hospitals and health-care institutions should revise their surgical policies to exclude specimens removed during arthroscopic ACL reconstruction and partial meniscectomy from mandatory gross and/or histological examination," write the authors, led by Joseph W. Greene, M.D., from the Insall Scott Kelly Institute for Orthopedics and Sports Medicine in New York. "Patients with intra-articular tumors, synovial disease, or atypical appearances who are undergoing knee arthroscopy would benefit from histological examination, but this could be determined by the orthopedist during surgery."

Takeaway: As hospitals look for opportunities for savings through elimination of unnecessary care, pathological examination of tissues from orthopedic procedures may be one source of cost savings, as studies show the exams rarely yield results that affect patient care.

Molecular Diagnostic to Make Laser Eye Surgery Safer

Avellino Lab (Menlo Park, Calif.) recently launched Avellino DNA Dual Test for LASIK Safety, a genetic test that can detect for both types of granular corneal dystrophy (GCD1 and GCD2). Patients with these corneal opacity conditions experience serious post-surgery vision complications. Such genetic testing is performed in the vast majority of patients prior to corrective laser surgery in parts of Asia, and the company hopes to make the test part of routine practice in the United States too.

GCD1/2 usually develops slowly, but if a patient with the condition undergoes vision correction (LASIK, LASEK, PRT, phototherapeutic keratectomy, and corneal transplant), they are at extreme risk of experiencing eventual blindness. While physicians can diagnose the condition with visual examination and family history in some cases, physical symptoms of the condition may not be present until later in life, putting unsuspecting patients at risk if they undergo the surgery. There is no cure for GCD, but the Avellino DNA Dual Test can detect the presence of the genetic mutation, allowing the patient to take precautionary steps to postpone the progression of the condition, including forgoing vision correction surgery and using ultraviolet protective lenses.

The test involves a cheek swab sample that is sent to Avellino Lab USA's CLIA-certified laboratory. Results are returned to the ordering physician within 24 to 48 hours. Avellino Lab has found the prevalence of GCD to be one out of every 1,078 refractive surgery candidates (based on 430,000 patients tested). This type of genetic test is the standard of care in Asia, where the company says that 80 percent to 90 percent of vision correction surgery candidates in Korea and Japan are tested. However, the company acknowledges the practice is not yet widespread in other parts of the world.

"Although it is not yet standard-of-care in North America, the U.S./Canadian market now ranks third behind Korea and Japan for genetic testing of laser vision correction candidates," Weston Nichols, Avellino Lab USA's sales and marketing director, tells *DTET*. "This growth trend likely means that genetic testing will become standard-of-care [included in guidelines] during the next few years."

The test is not currently reimbursed by Medicare or private payers but is "affordable," the company says. Nichols says the test represents a small fraction of the total cost of

laser vision correction surgery, so many clinics are choosing to incorporate the test into the total cost of the surgery.

Takeaway: The Avellino DNA Dual Test for LASIK Safety is yet another indicator of how genetic testing is permeating routine practice in a wide variety of medical specialties, now including ophthalmology. Avellino Lab's experience with clinics incorporating the test's costs into the total cost of surgery illustrates a trend toward bundled costs of patient care.

miRNA in Semen a Better ID of Prostate Cancer Than PSA

MicroRNA (miRNA) found in seminal fluid (SF) may be a diagnostically useful maker of prostate cancer, according to a proof-of-principle study published online ahead of print May 23 in *Endocrine-Related Cancer*. If, with further validation, these biomarkers continue to show that they that can accurately identify prostate cancer at an early stage and identify aggressive disease subtypes, it would be an important step in improving patient management, the authors say.

Using small RNA sequencing (Illumina's TruSeq Small RNA work-flow) and quantitative real-time polymerase chain reaction, the Australian researchers analyzed the RNA population in the nonsperm cellular portion of SF. In the discovery phase, comparisons were made between RNA men with low- or intermediate-risk cancer and men without cancer. All had elevated prostate-specific antigen (PSA) levels. Identified miRNA biomarkers were then validated in a subsequent cohort of 26 men with biopsy-proven, low-high risk tumors and 22 men with elevated PSA, but no detectable cancer on biopsy.

The researchers found that the RNA of the nonsperm SF cellular fraction consisted primarily of transfer RNA (tRNA) and miRNA, with a higher ratio of tRNA to miRNA among men with cancer compared to controls. A filtering strategy applied to robustly expressed miRNA identified 82 miRNAs that were differentially expressed in prostate cancer (20 increased and 62 decreased). Applying the potential miRNA biomarkers (those elevated in PCa) to the validation cohort showed five miRNA markers were present at significantly higher levels in cancer samples.

All of the miRNAs were able to more accurately discriminate between cancer and non-cancer than serum PSA, although miR-200b was the only significantly discriminatory marker. An additive diagnostic benefit of multiple miRNAs was lacking. Furthermore, none of the miRNAs correlated with serum PSA levels. The combination of miR-200b and serum PSA was significantly better at identifying men with cancer than PSA alone.

"SF miRNA measurements could be used to help determine if or when to proceed with curative interventions by providing an additional measure of global prostatic pathology, with a clear advantage of repeated and non-invasive sampling," write the authors, led by Luke A. Selth, from University of Adelaide in Australia. "SF miRNAs could be used in combination with other emerging molecular tools, such as urine TMPRSS2:ERG and PCA3, to provide a more robust appraisal of the likelihood of clinically significant disease. Second, SF miRNAs could have a role as a non-invasive tool for monitoring men in active surveillance regimens, a management approach now adopted worldwide for low risk prostate cancer."

Takeaway: While larger validation studies are warranted, prostate cancer experts are encouraged by the complimentary diagnostic benefit afforded by miRNA from seminal fluid.

G2 Insider

Patients Place Too Much Confidence in Prognostic Gene Profiles . . . Breast cancer patients tend to overestimate the "truth-value" of gene expression profile (GEP) tests by placing too much confidence in the tests' validity due to their own emotional needs at the time, according to a study published in *Current Oncology*. The authors say the study's findings point to the need to improve patient understanding of these tests and their limitations, given the impact of test results on clinical decisions.

Several GEP tests have been validated as prognostic for distant disease recurrence and predictive of the benefit of adjuvant chemotherapy for patients with estrogen receptor–positive disease. These test results affect treatment decisions both recommended by oncologists as well as patient preferences. The study relied on focus group (n = 4) and individual telephone interviews (n = 24) with early-stage breast cancer patients who used GEP testing conducted using semistructured discussion guidelines.

The researchers found that most patients (68 percent) did not undergo chemotherapy, largely because of the GEP test results. Patients' understanding of GEP testing was variable, and misapprehensions were common, including about how laboratories conduct analysis. Participants understood that the test would indicate whether chemotherapy would be beneficial in their care but generally did not understand that their results were founded on population-based statistics and were not uniquely personal to them. Additionally, responses indicated faulty interpretation and confused accounts of numbers, charts, and graphs showing recurrence risks.

Responses indicated that patients valued the test because it provided them with "certainty amidst confusion, with options and a sense of empowerment, and with personalized, authoritative information." The authors say patients commonly believed that the test was better and fundamentally different from other clinical tests. This kind of "magical thinking" was derived from an inflated sense of the test's validity, with many patients acknowledging they had "willingly suspended critique."

The authors say that the patients' need for reassurance about their treatment choices contributed to the overwhelming trust in the test. Respondents indicated that GEP test results were the primary deciding factor in treatment decisions, even patients who were initially reluctant to undergo chemotherapy.

"A type of 'magical thinking' underpinned their perceptions of the test, which was founded on a belief that GEP testing had unique scientific power and, therefore, truth-value," write the authors, led by Yvonne Bombard Ph.D., from University of Toronto in Canada. "Very few question[ed] or even discuss[ed] the test's potential limitations with their oncologist. When prompted to think about why they hadn't considered the possible limitations of the test, several participants identified emotional reasons for not doing so." G2

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