G2 INTELLIGENCE

Diagnostic Testing & Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

Issue 9-13/September 2013

CONTENTS

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NIH Funds Project Examining Impact of Sequencing Information

Researchers hope that a new study on whole-genome sequencing (WGS) will yield new insight into how this information should be delivered and how it is being used.

The Kaiser Permanente Center for Health Research (Portland, Ore.) recently won an $8.1 million National Institutes of Health (NIH) grant to study the use of WGS for preconception carrier screening. The project will explore the impact of WGS information on patients. Study participants will be members of Kaiser Permanente in Oregon and Washington who already have an order from their provider to receive preconception genetic testing. Researchers will use WGS to look for recessive genetic mutations for about 100 rare conditions—some of which can be fatal in children, like Tay-Sachs and Canavan diseases, and others like Pendred and Usher syndromes that affect hearing and vision. Throughout the study, couples will be asked to fill out surveys about their experiences, including what information was most helpful, how they want the information presented, and how they use the data.

"Some prospective parents will want information about each of these conditions, but others will only be interested in learning their risk for some of the more serious diseases," said Benjamin Wilfond, M.D., from Seattle Children's Research Institute, the study's co-principal investigator, in a statement. Additionally, incidental findings that meet criteria for actionability and validity will be returned to the patients, the researchers say.

While WGS has the potential to aid in diagnosis of serious disorders, additional evidence is needed to understand how WGS data should be reported. For more information on the return of WGS findings, please see *Inside the Diagnostics Industry* on page 5.

Siemens Focuses on Testing Smarts and Speed

"Test smarter, run faster." That was the motto of Siemens Healthcare Diagnostics (Tarrytown, N.Y.) at the American Association for Clinical Chemistry and American Society for Clinical Laboratory Science 2013 Annual Meeting and Clinical Lab Expo, held July 28-Aug. 1 in Houston. *DTTR* sat down with CEO Michael Reitermann to get his view of the marketplace, the company's latest platform, and how smarts and speed square with emerging technologies.

Continued on p. 2

▲ **Siemens Focuses on Testing Smarts and Speed,** *from page 1*

Michael Reitermann, CEO, Siemens Healthcare Diagnostics

What macro trends are you observing in the diagnostics industry?

On a global scale, among the inherent growth drivers for our business are demographics and the aging population. From our perspective, these will continue to create a favorable climate for our industry. Then there are different trends when we look at the United States. There is huge pressure on the health care system, and one of the manifestations of that is the pressure on reimbursement.

How do you see the implementation of the Affordable Care Act affecting the diagnostics space?

I associate the [Affordable] Care Act with moving from a pay-per-procedure to a pay-per-insured-life perspective—or population-based insurance—and that has certain impacts on our industry. I believe that, hopefully, it will be a positive impact, because now diagnostic testing and early detection is much more in the interest of the stakeholders.

Here at AACC, Siemens has launched the VersaCell X3. What new capabilities does this new automated platform offer?

The VersaCell X3 is an evolution. We have more variety, more flexibility with the systems that you can attach to it. We have improved the functionality. The new one-touch interface is much easier to use . . . because we also hear that there is a huge demand for experienced lab technicians. And these improvements make it easier for somebody to ease into the profession. Last but not least, you can connect it to our CentraLink [data management system], from the middleware, which allows you to intelligently communicate and direct the traffic in the lab. I'm optimistic that this will bring automation to a new segment and will allow smaller labs—or large labs that want to use it for specialty testing—to think differently about automation.

What is driving the growth within Siemens' Laboratory Diagnostics business?

New immunoassays are a big growth driver—one of them being vitamin D, which in the last two years has been a great addition to the assay portfolio. Point-of-care is one of the interesting growth opportunities, because in that field, when you look at the trends from a care provision perspective, there is a priority to keep patients out of the hospital, or when they come in the hospital, to quickly make decisions as to whether they need to be admitted. Take the example of chest pain, where a fast troponin test in the ER can help clinicians make critical decisions based on facts. And this is where our point-of-care portfolio can make a difference.

Siemens Healthcare recently announced a companion diagnostics partnership with Johnson & Johnson unit Janssen Pharmaceutica. Is this an area that you plan to continue expanding?

Drugs are getting more expensive and are becoming more targeted, so I believe the area of companion diagnostics will continue to develop. We have three partnerships announced and are working with other players that we will announce partnerships with at the right point in time. It's also a great opportunity also to expand our assay menu. And the platforms on which those assays will be delivered—whether it's kPCR, NGS, immunoassays—will depend on what platform is most suitable for the different endeavors. G2

Novel Mix of DNA, Inflammation Markers May Predict Cardiac Risk

Markers of cell death and formation of neutrophil extracellular traps (NETs) are independently associated with coronary artery disease (CAD) severity and occurrence of adverse cardiac events, according to a study published July 1 in *Arteriosclerosis, Thrombosis, and Vascular Biology*. A novel combination of these biomarkers could potentially aid in the prediction of cardiovascular risk in patients presenting with chest discomfort, the authors say.

Data were analyzed from 282 patients (median age 60 years) with nonacute chest discomfort and suspected CAD who were referred for outpatient cardiology evaluations. Coronary computed tomographic angiography (CCTA) was used to assess atherosclerosis, while in vivo markers of atherosclerosis progression (plaque and thrombotic debris, cellular constituents from the vessel wall, and cell types associated with inflammatory processes) were analyzed in blood.

Patients with severe CAD or abundant coronary artery calcification had significantly greater circulating extracellular double-stranded DNA (dsDNA) compared to individuals with no angiographically detected CAD. High plasma nucleosome levels were significantly independently associated with more than a two-times increased risk of severe coronary stenosis. The number of atherosclerotic coronary vessels and the occurrence of major adverse cardiac events were also independently predicted by markers of NETs, including MPO-DNA complexes. Finally, increased baseline levels of circulating dsDNA, nucleosomes, and markers of NETosis were significantly associated with the occurrence of major adverse cardiac events (MACE) during follow-up.

"These novel biomarkers could potentially aid in the prediction of MACE in patients with chest discomfort," write the authors, led by Julian Borissoff, M.D., Ph.D., Harvard Medical School (Boston). "Since some of these biomarkers are inexpensive and technically simple to determine, a broader role might be considered even prior to CCTA, if proven useful as diagnostic and prognostic tools."

If the markers do pan out, they have the potential to help doctors more efficiently identify which patients with chest pain are likely to have CAD, Borissoff said, possibly minimizing the currently used, time-consuming, and costly battery of tests.

Takeaway: With further proof, a novel combination of extracellular DNA, indicators of cell death, and inflammatory markers may form the basis of a new test capable of identifying chest pain patients at highest risk for clinically significant CAD. Clinical use of such a test has potential value in its ability to more rapidly and cost-effectively identify patients in need of further work-up or intervention.

Repeat Lipid Testing Often Ordered Unnecessarily

One-third of patients with coronary heart disease (CHD) who have met target goals for low-density lipoprotein cholesterol (LDL-C) have repeat lipid panel tests, according to a study published online July 1 in *JAMA Internal Medicine*. The authors say that this unnecessary testing in patients who have received no treatment intensification represents an overuse, and possibly a waste, of health care resources.

The researchers analyzed medical record and prescription data from 27,947 patients with CHD treated in a primary care clinic in a Veterans Affairs (VA) network of seven medical centers. All patients had achieved LDL-C levels of less than 100 mg/dL with no intensification of lipid-lowering therapy in the 45 days after the index lipid panel. Nearly one-third of patients (32.9 percent; n=9,200) had additional lipid assessments during the 11 months of follow-up. Among the 13,114 patients who met the optional LDL-C target level of less than 70 mg/dL, repeat testing was performed in 62.4 percent. There was a mean of 1.38 additional panels performed per patient, totaling an additional 12,686 repeat panels. Based on VA cost data, the mean lipid panel cost was $16.08, for a total of $203,990 in additional annual direct costs.

"This well-conceived study . . . delivers an important message regarding a type of waste that is likely widespread in health care and that goes under the radar because it involves a low-cost test," writes Joseph Drozda Jr., M.D., from the Center for Innovative Care (Chesterfield, Mo.), in an accompanying editorial. "However, it is precisely these low-cost, high-volume tests and procedures that need to be addressed if significant savings from reduction of waste are to be realized."

Over one-third of the repeat panels (34.2 percent) were performed within six months of the index test, and 79.9 percent were performed within nine months of the index lipid panel. Results of the repeat tests were "strikingly similar" to the index lipid panel results, suggesting that major medication or therapeutic lifestyle changes were not the drivers of repeat lipid testing, the authors say. Additionally, based on the results of the repeat lipid panel, in the 45 days following the repeat test, only 6.5 percent of patients were prescribed treatment intensification. Patients with a history of diabetes mellitus and/or hypertension, an increased burden of illness, and those with more frequent primary care visits were more likely to undergo repeat testing, when adjusting for facility-level differences.

"This points toward a tendency of health care providers to order frequent laboratory testing in complex patients," write the authors, led by Salim S. Virani, M.D., Ph.D., from Baylor College of Medicine in Houston. "Frequent lipid testing in these patients likely represents providers' practice to order comprehensive laboratory tests (including lipid levels) rather than focusing on one clinical issue (eg, ordering glycated hemoglobin measurement to assess diabetes control)."

Takeaway: In a health care environment increasingly focused on containing costs, laboratories need to play an important role in improving the stewardship of limited health care resources. Through education efforts and electronic ordering systems, laboratories can aid clinicians in ensuring appropriate test utilization, in part by boosting efforts to reduce redundant testing. G2

G2 INTELLIGENCE
Inside the Diagnostics Industry

Labs Begin to Implement ACMG's Incidental Findings Recommendations

The American College of Medical Genetics and Genomics' (ACMG's) April recommendations for the reporting of incidental findings uncovered in the course of clinical whole-exome and -genome sequencing kicked off a firestorm of debate pitting laboratories' duty to report versus a desire to preserve patient autonomy. While heralded as a starting point for establishing a common foundation for reporting clinical sequencing findings, the recommendations were also criticized as being premature given a lack of evidence on the frequency of incidental findings and patient preferences.

In an investigation of how laboratories are addressing the recommendations, *DTTR* found that most laboratories are still allowing for patients to opt out of reporting but that all laboratories have provisions for reporting incidental findings. Experts are viewing these recommendations as a first attempt to address the ethical and practical issues of reporting incidental findings but expect standardization of sequencing analysis and reporting practices to evolve over the coming years as penetrance of variants is better understood, nongeneticist clinicians are more comfortable with incorporating genomics into medical practice, and practical considerations such as reimbursement, genomic data storage, and consent issues are worked out.

Experts are viewing these recommendations as a first attempt to address the ethical and practical issues of reporting incidental findings but expect standardization of sequencing analysis and reporting practices to evolve over the coming years.

The recommendations call for mandatory reporting of a minimal set of incidental findings, where early intervention is likely to reduce or prevent serious morbidity or early mortality, in all patients, regardless of age or reason for the initial investigation. The initial set of variants to be added to examinations covers 57 genes for 24 conditions, including mutations known to increase risk of breast cancer, ovarian cancer, Lynch syndrome, and colorectal adenomas. While ACMG estimates that only 1 percent of patients who undergo genomic sequencing will have one of those mutations, concerns over mandatory reporting center on two key issues: the true pathological significance of the incidental findings and patient autonomy.

Variant Penetrance

Curation of the list of variants to be subjected to mandatory interrogations is based on the premise that early intervention improves outcomes.

"The rationale for our recommendations was that not reporting a laboratory test result that conveys a near certainty of an adverse yet potentially preventable medical outcome would be unethical," writes the ACMG in its May clarification of its original recommendation. "We agree that variants of unknown significance, variants associated with low or unknown penetrance, and variants associated with disorders not currently amenable to intervention should not be reported."

Objections to the preliminary variant list arise from the uncertainty concerning the penetrance and pathogenicity of the selected variants in the general population.

"Until well-curated human mutation databases are available, patients may be told about many mutations that, because of incomplete penetrance and misclassification

of benign variants as mutations, are likely neither to cause disease nor confer substantial risk when ascertained in the general population," writes Robert Klitzman, M.D., from Columbia University in New York, in a July 24 *Journal of the American Medical Association* (*JAMA*) viewpoint opposing ACMG's recommendations.

Given the risk of significant false positives, ACMG calls for "a very high bar [to] be set with return of only those variants with a very high probability of being deleterious" and guides sequencing laboratories to be cognizant of whether their tests have adequate coverage in all of the 57 genes to be screened. In their guidance for laboratories, ACMG says they recognize that some sequencing-based tests may not be optimized for coverage of these variants and that they "do not recommend that laboratories modify these tests if they are otherwise suitable to achieve their clinical objectives." Rather ACMG suggests laboratories report to the clinician that "the test was not optimized to detect incidental findings."

Patient Preferences

The best way to report incidental findings to clinicians and how they are in turn conveyed to patients are subject to ongoing refinement. Researchers continue to examine best practices and implications of returned results in both clinicians and patients. Such research was included in the July awards of $27 million in grants from the National Human Genome Research Institute's Clinical Sequencing Exploratory Research program.

While ACMG's recommendations do not allow for patients to opt out of the laboratory's reporting of incidental findings to the ordering clinician, the group's subsequent clarification did call for "the provider and patient [to] participate in a shared decision-making process regarding the return of results" with the clinician contextualizing these findings "to the clinical circumstances (e.g., the nature of ongoing clinical problems, knowledge of personal and family history, patient preferences, etc.)."

"The rationale for our recommendations was that not reporting a laboratory test result that conveys a near certainty of an adverse yet potentially preventable medical outcome would be unethical."
—ACMG

This perceived softening, however, did not appease outcries that mandatory reporting was violating patients' rights, causing questioning of whether or not these variants even fit the definition of incidental.

"To date, the traditions of genetic testing and reporting have exceptionalized all genetic risk information as potentially dangerous to the well-being of patients. This tradition, in the era of genome sequencing, must be reconsidered," writes Robert C. Green, M.D., from Brigham and Womens Hospital in Boston, in a *JAMA* viewpoint supporting ACMG's recommendations. "Incidental findings in clinical medicine are often mischaracterized as unintentional observations. However, a better characterization would be that such findings are potentially important observations noted during systematic examination by those with appropriate training."

Green and colleagues cite the analogy of when a radiologist uncovers abnormalities in a chest X-ray not related to the intended evaluation of a possible rib fracture.

"Radiologists are specifically trained neither to report every conceivable finding, nor to stop after satisfaction of search reveals an indicated finding. Rather radiologists use professional standards to assess and report a subset of unexpected findings that are likely to be medically important," they write.

But in yet a third *JAMA* viewpoint on the recommendations, Lainie Friedman Ross, M.D., Ph.D., from the University of Chicago, and colleagues further debate the definition of incidental.

"Any positive findings from these additional analyses are hardly incidental; they are the results of a new recommendation for mandatory testing beyond the scope of the original request that will require a significant amount of time, effort, and resources," write Ross and colleagues. "This approach is similar to requiring a laboratory to test every blood sample for human immunodeficiency virus, hemoglobin A1c level, and 54 other tests for which early treatment can reduce morbidity or mortality, even if the physician had only ordered, and the patient had only consented to, a cholesterol measurement."

While ethicists will continue to debate the definition of *incidental findings*, laboratories are interested in the more practical issues, including consent.

Considerations for Labs

Based on conversations with experts in the field, *DTTR* uncovered that the majority of laboratories, like Medical College of Wisconsin's Human and Molecular Genetic Center, are maintaining some form of an opt-in, opt-out option for incidental findings. It appears as if all exome sequencing laboratories are equipped to report on, or are preparing to report on, at least the variants listed in the ACMG recommendations, with some reporting on incidental findings beyond the scope of the recommendations.

"It would be unrealistic to propose to every patient undergoing a physical examination, laboratory testing, or radiological procedure that they consent in advance to the panoply of low-probability findings that might be discovered, or that the clinician, radiologist, or laboratory be required to mask or delete such findings from the report because a patient might be fearful of their discovery," writes Green. "Categorical statements of preference such as tell me about treatable conditions, but not untreatable conditions will never be adequate to guide the management of incidental findings in genomic sequencing because the value of the incidental finding to the health of the individual patient, like any other laboratory value, cannot be accurately assessed until it is clinically contextualized for that patient."

"We have seen patients from every economic and socioeconomic background and they are not all Ph.D.s and in general they do think carefully about it and understand what they are choosing."
—David Bick, M.D.

Taking the individual patient's circumstances into account has led some laboratories to maintain their opt-out positions when it comes to incidental findings.

"After serious reflection and discussion we concluded that the patients and family are in the best position to decide what to do with their results," says David Bick, M.D., medical director of genetics at Childrens Hospital of Wisconsin. "Our experiences with patients are divergent from the college. In our experience families do understand what they are choosing. We have seen patients from every economic and socioeconomic background and they are not all Ph.D.s and in general they do think carefully about it and understand what they are choosing."

Practically, Bick says the workload of counseling patients and families has been reduced significantly with experience. Based on initial experiences, other experts also say the

incremental workload is light given current volumes, but reimbursement remains a big uncertainty for laboratories in implementing ACMG's recommendations.

Pinar Bayrak-Toydemir, M.D., Ph.D., medical director of the molecular genetics laboratory at ARUP (Salt Lake City), tells *DTTR* that since adopting recommendations ARUP has not found anything incidental to report after doing "tens of exomes." She says that following ACMG's recommendations might add a few hours of interpretation work (and additional time for confirmatory Sanger sequencing if any incidental findings were discovered), but the turnaround time on exome sequencing is already so long that the incremental work doesn't really impact it. As far as reimbursement, she says there is currently no method to seek compensation for the additional variants.

"In the long run, genome sequencing has the potential to bring down costs, as it queries the whole genome at less of a cost than many single gene tests," says Michael Watson, Ph.D., ACMG's executive director. "ACMG is working with government regulators as well as third-party payers on both the new CPT codes for molecular pathology and the reimbursement rates that have been proposed by the Medicare carriers. At the time those codes were submitted to the American Medical Association's CPT panel, there was no expectation that there would be a recommendation for reporting of incidental findings. As more laboratories begin to offer the incidental findings as a part of their testing, a new genome sequencing CPT code would need to be proposed to the CPT panel that included reporting of these findings."

While clinical sequencing continues to permeate clinical practice and laboratories gain experience to draw from in informing future iterations of practice standards, ACMG has been lauded for kick-starting the dialogue.

"I think the ACMG did an excellent job staring the discussion, but I strongly believe this discussion is a topic requiring wide discussion, not just among laboratory directors and physicians, but it must include the public," says Bick. "WGS won't be acceptable to the public if their wishes are not respected."

Takeaway: Many ethical and practical considerations remain unresolved relating to the reporting of WGS findings. Laboratories are currently inclined to not fully adopt ACMG's recommendations and instead maintain the ability for patients to opt out of reporting of incidental variants.

Sampling of Laboratory Policies

- **Ambry Genetics** (Aliso Viejo, Calif.). The ACMG secondary findings minimum list is offered as default. However, as part of the standard consent form, patients can decline receipt of all secondary findings. Ambry will retain the original secondary findings options, which will allow for the expanded secondary finding reports.
- **ARUP** (Salt Lake City). ARUP has implemented ACMG's recommendations with all individuals undergoing exome sequencing receiving a separate report indicating if any pathogenic mutations were detected based on the ACMG recommended list of genes.
- **Baylor College of Medicine** (Waco, Texas). For medically actionable incidental findings Baylor currently does not offer an opt-out. However, Baylor requires an opt-in for an extended report of additional incidental findings.
- **Columbia University Personalized Genomic Medicine Laboratory** (New York). Columbia maintains an opt-in or opt-out for incidental findings related to cancer predisposition syndromes and life-threatening conditions.
- **Emory University Genetics Laboratory** (Atlanta). Emory is said to be evaluating its policy, but at this point mutations involving childhood onset conditions will be reported for genes, even if they are unrelated to the patient's disease. Patients or guardians can opt in or out for carrier status for autosomal recessive conditions, pharmacogenetic variants, adult-onset medically actionable, and adult-onset not currently medically actionable (for adults only).
- **Medical College of Wisconsin's Human and Molecular Genetic Center** (Milwaukee). HMGC automatically reports treatable childhood onset disorders but maintains an opt-in or opt-out for other incidental findings.
- **Partners Healthcare Laboratory for Molecular Medicine** (Boston). Unless noted on the requisition, a general genome report containing results that may be unrelated to the indication for testing, but may be of potential medical value, is included. This report contains a summary of secondary findings for highly penetrant monogenic disease risk, carrier status for recessive disorders, and pharmacogenomic results. Patients may choose to receive an incidental findings report limited to the minimum genes and diseases recommended by the ACMG.

Lessons Learned in Establishing a Clinical Sequencing Lab

In 2009, the Medical College of Wisconsin (MCW; Milwaukee) became one of the first in the nation to utilize whole-genome sequencing (WGS) for clinical, diagnostic purposes in patients unsuccessfully resolving diagnostic odysseys.

In an invited commentary published July 17 in *Science Translational Medicine*, the founders of MCW's Human and Molecular Genetic Center (HMGC) discuss lessons learned in converting a sequencing laboratory designed for research into a clinical program. They offer guidance regarding the practical, technological, economical, and ethical considerations that other laboratories planning their entry into clinical WGS and whole-exome sequencing must address.

The genomics medical clinic successfully sequenced and diagnosed its first patient in 2009 in collaboration with Children's Hospital of Wisconsin and Froedtert Hospital. However, the seed was planted for opening a clinical sequencing laboratory back in 2004 when Howard Jacob, Ph.D., HMGC's director, and colleagues undertook a $100 million, two-year project to sequence a rat genome. Noting the significant improvement in sequencing efficiency from the $1 billion, 10-year human genome sequence, Jacob and colleagues thought it would be reasonable to assume that genome sequencing would be in the clinic by 2014, he tells *DTTR*.

"Our clinical program is built around the principal idea that making a diagnosis is essential, even in cases where the results may not lead to better treatment" but can change the management plan for the patient, the authors write.

To date MCW's HMGC has sequenced more than 30 whole genomes and 70 whole exomes, primarily in children, yielding a definitive diagnosis in roughly 27 percent of cases for rare or undiagnosed diseases. The center suspects that in some of the 73 percent of unsolved cases WGS has identified the correct variants but there is currently no evidence in the literature supporting causality or clinical significance.

Jacob says that while some definitive lessons have been learned, with each case HMGC continues defining and redefining its program.

"Our initial concerns were cost and data accuracy, but the major challenges turned out to be the logistics of delivering genome sequence information to clinicians, how clinicians use the data, and how patients and their families deal with the secondary [incidental] findings," the authors write in the paper. Jacob adds that while "with each case we have done we have learned something, we hope to get to a point where it is turnkey."

While some have argued for a strategy of outsourcing WGS to expert centers, the authors suggest that WGS will become more widespread in part because of advantages associated with local execution, including speed, compliant data storage, and easier interactions with the clinical team. The initial challenge, they say, will be overcoming clinicians' perception that WGS is an expensive, nonuseful clinical tool. While recognizing that each integrated genomic medicine clinic will face some institution-specific considerations, the authors cite the following practical considerations for other labs to consider.

Legal Compliance. New clinical genomics laboratories need to identify state and local laws and hospital guidelines that affect storage of clinical or laboratory data and samples. Future guidelines are expected to clarify the types of genomic sequence

data that need to be disclosed to the patient and stored. (For more information on the returning of incidental findings, please *Inside the Diagnostics Industry* on page 5.)

Workflow. Clinical application of WGS involves multiple personnel, including genetic counselors, clinical geneticists, pathologists, clinical laboratory personnel, bioinformaticians, and the ordering clinician. The founders of HMGC believe the ideal solution develops across departments to integrate all needed personnel and expertise.

Analytical Processes. In clinical laboratories, clinical processes must be documented and validated. MCW has required some significant alterations to existing protocols, given that HMGC began as a research laboratory.

"In a research lab it is a different mind-set. As part of the research, protocols are modified and evolve as [researchers] discover it is faster to do it one way or another," Jacob says. "As a clinical lab you must lock down the protocols and there can't be deviations. There is no difference in the technical abilities of the techs, it is just a different mind-set."

In order to obtain Clinical Laboratory Improvement Amendments certification and College of American Pathologists accreditation, HMGC developed and wrote 1,192 pages of standard operating procedures. HMGC also developed an in-house, tertiary analysis platform called CarpeNovo that is updated and revalidated every six months (a process that takes four weeks to six weeks).

Clinician Education. Successful implementation is dependent upon clinicians seeing the value in WGS. "We built this clinic with clinicians based on what type of information they needed," Jacob explains. "To tell them this will change medical practice in 10 years doesn't help them with the patient they are going to see in 15 minutes."

Integrating Data. Electronic health records are currently not equipped to integrate comprehensive clinical and phenotype patient profiles with the variants discovered in the patient's genome. To address these needs, MCW created an in-house software (ClinMiner) to integrate data sources and reporting languages.

Reimbursement. While the cost of sequencing is expected to further decline, most insurers, including Medicaid, Medicare, and many private payers, will not yet pay for WGS. HMGC says they have had "some success" by demonstrating that the cost of sequencing one whole genome is more economical than ordering multiple genetic tests.

"There is a lot of discussion of why it won't work except for a few diseases and the cost. But the way I see it, it is not if [WGS] will change medicine, it is when. There is value in the genome to you, your family, and to society," says Jacob. "People get uncomfortable because there are no easy answers—you can't pull this off the web. Instead of thinking why not to do it, partner with someone. We challenge the fence-sitters to do 20 cases of their own and see whether WGS adds value to clinical decisionmaking. I would be shocked if a laboratory does 20 and doesn't continue with it."

Takeaway: Whole-genome sequencing will permeate clinical medicine, initially primarily in cases of patients who have unsuccessfully undergone a diagnostic odyssey. While delivering genome sequence data to clinicians remains a challenge requiring institution-specific development of information solutions, the value WGS adds to clinical decisionmaking and an improving economic case will further sway early adopters.

Host Gene Expression Signatures Can ID Infectious Pathogens

Newly identified blood transcriptional profiles can distinguish between children with fevers from viral infection and those from bacterial infection, according to a study published online July 15 in the *Proceedings of the National Academy of Sciences*.

Using the distinctive profiles to analyze host response can also identify children whose viral infection is nonpathogenic, concludes the study. This information can potentially supplement nucleic acid amplification pathogen detection methods to improve treatment decisions and antibiotic stewardship.

"Studies on host blood transcriptional profiles can be considered as a paradigm shift, providing clues about infectious pathogens through interrogation of host gene expression patterns," writes co-author Gregory Storch, M.D. "Host transcriptional analysis may prove to be a useful test method, supplementing sensitive pathogen-based nucleic acid amplification assays and also providing clues about etiology when no pathogens are confirmed from the direct detection of microbial pathogens."

The Washington University (St. Louis) researchers conducted expression microarray analyses on blood samples from 30 febrile children (aged 2 months to 36 months; positive for adenovirus, human herpesvirus 6, enterovirus infection or acute bacterial infection) and 22 afebrile controls. The ill children had fever above 104 degrees Fahrenheit but no obvious symptoms, like a cough or diarrhea.

The gene activity in white blood cells produced transcriptional profiles that clearly distinguished virus-positive febrile children from both virus-negative afebrile controls and afebrile children with the same viruses present in the febrile children. Virus-specific gene expression profiles emerged with viral infection in febrile children activating the IFN signaling pathway and bacterial infection activating the integrin signaling pathway. Because of overlap in patterns of pathway activation, pathway analysis was not useful for distinguishing specific viruses among febrile children. But host blood transcriptional signatures had superior predictive value than white blood cell count-based criteria in discriminating febrile children with viral from bacterial infection.

While presently gene expression microarray is not practical for bedside decisionmaking, investigators hope to identify a smaller number of genes that could be used to distinguish infection sources and evaluate a second-generation test in a broader population of children. Such a test could raise physicians' comfort in not prescribing antibiotics.

"Interestingly, the transcriptional profile of febrile children positive for HHV-6 or adenovirus was dramatically different from the profile of afebrile children positive for the same viruses, which was indistinguishable from the profile of virus-negative afebrile children," writes Storch. "This finding has potential practical importance, because the application of sensitive molecular viral detection tests to clinical medicine may detect asymptomatic as well as symptomatic infection and thus, has created a need to determine the clinical significance of the detection of viral nucleic acid in an individual patient."

Takeaway: Transcriptional profiling of host gene expression represents a shift in methodologies for diagnosis of infectious pathogens. With further refinement in the coming years the test may cheaply provide clinicians with enhanced information on the true pathogenesis of present viruses, thereby improving the appropriateness of antibiotic prescriptions.

G2 Insider

Single Viral Activity Test May Be Inadequate Before Immunomodulatory Therapy . . . A single antibody measurement of viral activity for the JC virus may not be sufficient to assess risk for the often fatal disease progressive multifocal leukoencephalopathy (PML) in patients receiving immunomodulatory therapies that have been shown to reactivate the virus, according to a research note published online June 6 in the *New England Journal of Medicine*. Given the finding that one-third of multiple sclerosis (MS) patients had viremia but tested seronegative suggests a more comprehensive risk-mitigation strategy involving periodic monitoring over the course of natalizumab treatment may be necessary, say the authors.

Plasma samples from separate cohorts of MS patients who received monthly infusions of natalizumab were analyzed for the presence of JC virus antibodies and viral DNA. Blood samples were obtained at baseline before the first infusion (n=26) and for several months during the first year of treatment as well as blood samples after more than 24 months of treatment (n=23). The researchers found that more than one-third (17 of 49 patients) had viremia at some point during the study. Viremia was present in 10 of 26 patients in whom treatment was initiated, including four who were seronegative (antibody titer, <2560) and six who were seropositive (antibody titer, ≥2560). Of these 10 patients, viremia was present at baseline in four and three were seropositive. Of patients who received more than 24 infusions, seven of 23 had viremia and two were seronegative. For comparison, blood samples from 18 healthy volunteers demonstrated that six were seronegative, 12 were seropositive, and none had detectable viral DNA.

"The relatively high percentage of patients who had viremia and were seronegative appears to be greater than the false negative rate identified previously," write the authors, led by Eugene Major, Ph.D., from the National Institute of Neurological Disorders and Stroke in Bethesda, Md. "To establish risk-stratification algorithms for PML in patients who receive potent immunomodulatory therapies, a single measurement of viral activity such as a test for antibodies to JC virus may be useful, but not sufficient to assess risk." G2

Company References

Ambry Genetics 949-900-5500

American College of Medical Genetics and Genomics 301-718-9603

ARUP Laboratories 801-583-2787

Baylor College of Medicine Genetics Laboratories 713-798-5767

Columbia University Personalized Genomic Medicine Laboratory 212-305-3053

Emory University Genetics Laboratory 404-778-8499

Kaiser Permanente Center for Health Research 503-335-2400

Medical College of Wisconsin's Human and Molecular Genetic Center 414-955-4887

Partners Healthcare Laboratory for Molecular Medicine 617-768-8500

Siemens Healthcare Diagnostics 914-631-8000