G2 INTELLIGENCE

Diagnostic Testing & Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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Changes in CSF Biomarkers Detectable Decades Before Clinical Alzheimer's

Pathophysiological changes in cerebrospinal fluid (CSF) biochemical markers are evident two decades before the onset of clinical symptoms in autosomal dominant Alzheimer's disease (AD), according to a study published in the Aug. 30 issue of the *New England Journal of Medicine*.

The researchers from the Dominantly Inherited Alzheimer Network analyzed clinical data in a prospective, longitudinal study of 128 participants with a family history of an early-onset, autosomal dominant form of the disease. Concentrations of amyloid-beta (Aβ)42 in the CSF appeared to decline 25 years before expected symptom onset. Fifteen years before expected symptom onset, levels of tau in the CSF were increased. The decrease in Aβ42 and the increase in tau in the CSF were similar to the changes typically observed in late-onset sporadic Alzheimer's disease.

"The definition of the timing and magnitude of pathophysiological changes associated with Alzheimer's disease has implications for the development and implementation of diagnostic and predictive tests and the design of prevention trials," conclude the authors, led by Randall J. Bateman, M.D., from Washington University School of Medicine in St. Louis.

For more on the search for predictive biomarkers for AD, please see *Inside the Diagnostics Industry* on page 5.

Specialized Market Emerging: Diagnostics Companies Establishing Presence in Biodefense

Since the 2001 anthrax attacks the federal government has invested substantially in biodefense. Over the past few years, experts say the federal government has shifted its biodefense development strategies away from agent- or bug-specific initiatives toward more flexible platform-based approaches. As the government continues to put a proposed $5.54 billion biodefense item in the 2013 fiscal year budget, diagnostics companies are increasingly well positioned to participate in government programs.

"The distinction between traditional biodefense (environmental surveillance) and detection of emerging infectious diseases has blurred as the agents of concerns are often the same," Amy Altman, Ph.D., vice president Luminex Biodefense, tells *DTTR*. "In addition, detection of either requires advanced technologies that are robust and proven. Given that diagnostic companies

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▲ **Specialized Market Emerging,** *from page 1*

are in the business of creating advanced technologies for in vitro diagnostic applications, it makes sense that the DOD would partner with these companies to develop technologies to serve their mission needs."

While funding continues to be split across multiple agencies (in the proposed 2013 budget the Department of Health and Human Services and the Department of Defense (DOD) continue to account for the majority of civilian biodefense funding with 72 percent and 15 percent, respectively), policy strategists are suggesting an interdisciplinary approach to biosurveillance will pay the biggest dividends. As was illustrated in the National Strategy for Biosurveillance released by the White House in late July, the government is calling to have a broader array of participants as well as prioritizing the development of a broader array of point-of-care diagnostics to expand surveillance efforts.

Ideally experts say these diagnostic and surveillance platforms will apply to a wide variety of threats from bioterrorism to infectious disease pandemics. Diagnostics companies including BioFire Diagnostics (formerly Idaho Technologies; Salt Lake City) and Luminex (Austin, Texas) have both been recipients of government funding and are continuing expanded development efforts of multiplex platforms capable of detecting multiple agents.

BioFire Diagnostics

As Idaho Technologies, the company received a DOD contract in 2003 to develop a field-deployable, multiplexing ploymerase chain reaction (PCR) system capable of identifying a range of biological threat agents. The company's RAPID family and the RAZOR-EX biosurveillance products are still commercially available. But the company's concerted move into clinical diagnostics exemplifies the flexible platform approach gaining interest in biodefense funding circles.

BioFire's FilmArray system is a self-contained, automated multiplexing PCR system cable of identifying up to 20 targets. The respiratory panel is currently available with U.S. Food and Drug Administration clearance and the company is in the midst of developing and validating three additional multiplex panels: the Blood Culture ID panel (tests for 20 bacteria, fungi, and antibiotic resistance), the gastrointestinal panel (test for bacteria, diarrheagenic E. coli/Shigella, protozoa, and viruses), and its Biological Threat panel (tests for 16 agents, some with multiple targets).

Luminex

In August Luminex was awarded an $11.6 million, three-year contract by the DOD's Defense Threat Reduction Agency. The funds will provide capital to develop a prototype of a field-deployable diagnostic tool capable of rapid detection of biothreat agents and patient response biomarkers indicative of systemic disease. The handheld system will be able to detect both protein and nucleic acid targets to diagnose Systemic Inflammatory Response Syndrome, which can result from blood infection by biowarfare. The device also has potential, the company says, for diagnosis of SIRS in noncombat environments and targeting of appropriate therapies.

"In the current austere budget environments, it makes sense for the DOD to leverage the technologies being developed for commercial markets.

One of the reasons that Luminex is well suited for work with the government on diagnostics is that our technology has been well validated," says Altman. "The DOD is able to benefit from technology development that has been done for a commercial market."

Earlier in the year Luminex had announced the company was going to make additional investment in biothreat and environmental detection applications.

Startup Plans to Revolutionize POC Testing With Protein-Engineered, Fluorescently Responsive Sensors

SenGenix (Durham, N.C.) is developing point-of-care diagnostic tests based on reagentless, fluorescently responsive sensors that the company says will deliver accurate, actionable results in seconds. The platform is based on protein-engineering technologies developed at Duke University (Durham, N.C.) and will offer a menu of two point-of-care tests initially for hospital use.

The company is currently embarking on a $3 million Series A round of financing that will enable the company to continue developing specific molecular sensors for each analyte and file some provisional patents. Additionally, the initial funding will allow the company to transition its protein engineering core laboratory from Duke and hire scientific and engineering staff.

Bioinformatics and automation-assisted protein engineering identify the proteins and allow for florescent molecules to be integrated into the protein. Fluorescently responsive sensors can be printed onto a test strip and read by a smartphone-sized reader to detect the clinical level of the desired analyte, allowing for speedier and cheaper detection with just a drop of blood. Analyte-specific fluorescently responsive sensors can be combined in different configurations to create panels of tests.

Lawrence Cohen, CEO of SenGenix, tells *DTTR* that the company will initially focus on a kidney panel and a basic metabolic panel consisting of the eight most commonly ordered tests: glucose, blood urea nitrogen, creatinine, sodium, potassium, calcium, chloride, and bicarbonate. The kidney panel will initially be used in radiology and emergency departments as a prescreening test for patients needing imaging using a contrast media to rule out kidney problems that will cause complications. The rapid results from the basic metabolic panel will "streamline emergency room workflow and will lead to faster triage decisions."

SenGenix believes the current U.S. market for the basic metabolic panel is $4.4 billion and hopes to capture at least 5 percent of the market to annual revenue of $200 million. In total the company says it will need to raise $27 million to bring the panels to market in the next four years. The system is expected to be a 510K cleared, CLIA-waived product consisting of the platform instrument and test panels. While final pricing has yet to be worked out, Cohen says he anticipates test charges to be roughly half of the reimbursable rate—approximately $6 for the basic metabolic panel and $3.75 for the kidney panel.

"The cost will help to convince the lab to be on our side," says Cohen. "Our market research shows that ER physicians like the product because they don't like waiting. Labs have previously said point-of-care costs more money so they just work to improve service. This system overcomes that barrier."

ScolioScore Prognostic Test Acquired by Transgenomic

In an effort to further bolster its position in personalized medicine, Transgenomic (Omaha, Neb.) in late August announced plans to buy the prognostic ScolioScore scoliosis test from privately held Axial Biotech (Salt Lake City) for $4.4 million in cash.

"The acquisition of ScoliScore furthers Transgenomic's strategic vision of investing in products and technologies with significant potential or that can benefit immediately from synergies available through our existing sales team, clinical laboratories and other infrastructure," said Craig Tuttle, Transgenomics' CEO, in a statement. "We believe that ScoliScore will contribute positively to earnings by the end of 2012, excluding any acquisition related charges."

As part of the deal, which is expected to close in September pending approval of Axial Biotech's shareholders, Transgenomic receives the global rights to the genetic ScoliScore Adolescent Idiopathic Scoliosis (AIS) Prognostic Test, including technology and intellectual property, as well as an established revenue and customer base.

AIS is diagnosed in 100,000 adolescent children annually, but only 2 percent to 4 percent of these patients will progress to severe spinal curve requiring surgery. Despite low progression rates, adolescents with scoliosis are routinely monitored by numerous physician office visits and frequent X-ray examinations. The saliva-based ScoliScore Test identifies with 99 percent accuracy, the company says, those individuals who are unlikely to progress, which can significantly reduce their radiation exposure.

New Entrant in the PGx Market for Psychiatric Drug Response

SureGene (Louisville, Ky.) and CLIA-certified PGXL Laboratories (Louisville, Ky.) commercially launched their collaboratively developed SureGene Test for Antipsychotic and Antidepressant Response (STA^{2}R) at the end of August. The developers say that the molecular pharmacogenetic test will aid clinicians with identifying potential tolerability or efficacy issues during drug selection, a notorious challenge in the field of psychiatry.

"We are a discovery company first. What differentiates us is our proprietary biomarkers," says Tim Ramsey, vice president of new product development at SureGene. "We are not launching a me-too product. We believe we have a superior product."

The STA^{2}R panel combines the propriety SULT4A1-1 genetic signature with analysis of four other genes including the serotonin transporter gene SLC6A4 and drug metabolism genes CYP2D6, CYP2C19, and CYP1A2. Clinical studies have found that SULT4A1-1-positive, schizophrenic patients treated with olanzapine have greater reduction in psychotic symptoms and a significantly lower risk of being hospitalized.

"We absolutely will continually improve the panel over time," says Ramsey. "We already have other things in the queue to incorporate into the panel."

The test is run in PGXL's laboratory using a cheek swab sample. Turnaround for the test occurs within a few days. PGXL says the panel will be billed using stacked CPT codes for the time being, and the company says it doesn't foresee any challenges since they are already routinely reimbursed for components of the panel.

G2 INTELLIGENCE
Inside the Diagnostics Industry

Blood-Based Alzheimer's Diagnostic Stymied by Difficulty Validating Biomarkers

While definitive diagnosis of Alzheimer's disease (AD) has progressed in recent years with the clinical use of cerebrospinal fluid (CSF) biomarkers and advanced imaging modalities, including PET scans and structural MRIs, diagnosis still primarily relies on clinical symptoms. A simple, cost-effective blood-based diagnostic test remains elusive yet appealing for both for diagnostic purposes and to monitor treatment response in drug trials.

High throughput multiplex platforms are helping researchers to identify potential predictive biomarkers, but the sheer volume of biomarker discovery studies and the inability to replicate findings have been barriers to development of a clinically useful test.

"A key limitation to progress has been a proliferation of markers without cross-validation among projects," wrote Sid E. O'Bryant, Ph.D., from the University of North Texas Health Sciences Center in Fort Worth, in an editorial published Aug. 28 in *Neurology*. "While the discovery of novel markers will continue to be of importance, it is imperative that currently identified putative markers be thoroughly investigated, lest the field be stuck forever in discovery science."

Barriers to Clinical Test Development

One can see an example of this feverish proliferation of biomarker discovery in the July issue of the *Archives of Neurology*. Published in the same issue were two independent studies reporting the discovery of two very distinct multi-marker panels that both groups concluded were a significant step toward a screening test.

> ***"While the discovery of novel markers will continue to be of importance, it is imperative that currently identified putative markers be thoroughly investigated, lest the field be stuck forever in discovery science."***
> ***—Sid E. O'Bryant, Ph.D.***

In the study conducted by the Alzheimer's Disease Neuroimaging Initiative (ADNI) and Australian Imaging Biomarker and Lifestyle Research Group (AIBL), researchers conducted a baseline plasma screening of 151 multiplexed analytes in a cohort of 754 healthy controls and 207 AD participants. The researchers identified an 18-biomarker signature panel for the diagnosis of AD in the AIBL cohort and validated them in the ADNI population. Among the markers, cortisol, pancreatic polypeptide (PP), insulinlike growth factor binding protein2 (IGFBP2), β2 microglobulin, vascular cell adhesion molecule 1 (VCAAM1), carcinoembryonic antigen, matrix metalloprotein 2, CD40, macrophage inflammatory protein 1α, superoxide dismutase, and homocysteine were signficantly increased, while apolipoprotein E, epidermal growth factor receptor, hemoglobin, calcium, zinc, interleukin 17 (IL-17), and albumin were significantly decreased in AD. Adding this biomarker set to age, sex, and APOE genotype improved the sensitivity and specificity from 77 percent to 85 percent. Reducing the set to just eight biomarkers (cortisol, IGFBP2, PP, IL-17, VCAM1, β2 microglobulin, epidermal growth factor receptor, and carcinoembryonic antigen) only reduced sensitivity and specificity by 2 percent.

The second study, conducted by researchers from the Biomarkers Consortium Alzheimer's Disease Plasma Proteomics Project (BCADPPP), also used an ADNI cohort. They found that increases in PP, enascinC, matrix metalloproteinase 1 (MMP-1), eotaxin 3, and N-terminal protein B–type brain natriuretic peptide (NT-proBNP) levels and decreases in IgM and apolipoprotein E (ApoE) levels were consistently observed across all group comparisons. Across models the markers had 80 percent to 90 percent sensitivity, and incorporating plasma analytes improved specificity from 40 percent to between 70 percent and 80 percent in its ability to differentiate patients with AD from healthy controls. The researchers also found a specific protein profile associated with ApoE allelic status.

"It is tricky working with blood biomarkers. AD is not directly in contact with blood in the same way as other organs, and changes in the blood may reflect risk factors or medications frequently used in the elderly."
—William Hu, M.D., Ph.D.

Experts caution that biomarker discovery is not enough and that markers need to be validated. Among some of the many factors complicating replication efforts are the possibilities that the observed changes in blood marker levels may be a function of concurrent medication use or comorbidities. Additionally, biomarkers may influence each other, "suggesting that many of the top biomarkers may be redundant and part of a larger common signaling cascade," considered the authors of the BCADPPP paper.

"In the literature over the last five years there have been a number of blood biomarker panels that have come and gone," says William Hu, M.D., Ph.D., an assistant professor of neurology at Emory University in Atlanta. "Initially exciting findings haven't been replicated in different populations or even in the same population at a different date. It is tricky working with blood biomarkers. AD is not directly in contact with blood in the same way as other organs, and changes in the blood may reflect risk factors or medications frequently used in the elderly."

While validation of identified biomarkers remains an undeniably large barrier necessary to overcome for successful development of a blood-based AD diagnostic, there are some optimistic signs emerging.

Encouraging results were recently published in the Aug. 28 issue of *Neurology* by Hu and a group of researchers representing ADNI. Using a targeted proteomic approach the group measured levels of 190 plasma proteins and peptides in 600 participants from two independent centers. They identified 17 analytes associated with the diagnosis of very mild dementia, mild cognitive impairment, or AD. Four of these analytes (ApoE, B-type natriuretic peptide, C-reactive protein, and pancreatic polypeptide) were also found at altered levels in a third cohort of 566 patients. These findings are significant, experts say, both because results were replicated across three independent cohorts and because the markers were related to CSF markers of AD.

Despite the encouraging results, Hu believes that based on the time it took for spinal fluid testing for AD and amalyoid imaging to move from reproducible results to actual clinical test, he expects it will be about 10 years before a blood-based diagnostic for AD will be clinically available. He cautions though, that simply having a diagnostic is not the end goal.

"There are some primary care physicians who say, what's the point of clinical screening. If there is no treatment, then why bother," Hu explains. "It's not [entirely about] the diagnosis. A diagnostic can lead to better treatment and knowing what the treatment is doing."

While biomarker discovery and analysis continues feverishly, debate still lingers regarding the ideal characteristics a blood-based diagnostic would need to encompass to be clinically acceptable. It is a trade-off between test accessibility and test accuracy, the experts say.

Ideal Characteristics of Hypothetical Diagnostic

Researchers from Bristol-Myers Squibb (Princeton, N.J.) evaluated different scenarios in hypothetical cohorts of 10,000 subjects to determine the ideal characteristics necessary to maximize the benefit of a potential Alzheimer's diagnostic. Potential test characteristics evaluated were low (70 percent) or high (90 percent) sensitivity and specificity, as well as tests that had low, moderate, and high levels of patient access/acceptability defined as 50 percent, 75 percent, or 95 percent, respectively. Their findings were presented at the Alzheimer's Association International Conference (Chicago; July 15-18).

"A test that is highly sensitive and specific—yet has significant barriers to patient access—will not achieve its potential and may become a major obstacle to appropriate care."
—David Budd

The researchers found access to a diagnostic (defined by test capacity, cost, and ease of administration) was as important for determining appropriate diagnosis and treatment as test accuracy. Tests that were both accurate and had high accessibility achieved the correct treatment decision in 83 percent of cases, 4 percent receiving false-positive diagnosis, and 14 percent of hypothetical subjects remaining undiagnosed. By comparison, if the accurate test had low accessibility, at least 67 percent of subjects would receive the correct diagnosis but at least 50 percent of subjects with AD would remain undiagnosed. In the opposite scenario of a test with low clinical accuracy but easy access, a nearly identical number of patients would receive the correct diagnosis (68 percent), while even fewer would remain undiagnosed (33 percent).

"A test that is highly sensitive and specific—yet has significant barriers to patient access—will not achieve its potential and may become a major obstacle to appropriate care," conclude the authors, led by David Budd. "Better treatment outcomes can be achieved with a lower-sensitivity, high-access test than with a high-sensitivity, low-access test."

Hu echoes some of these same sentiments, saying that using CSF markers and amyloid imaging, current diagnostic accuracy might be as high as 90 percent to 95 percent in specialty clinical settings, but that may not be available in Wichita, Kan. "The goal is not a definitive answer. If you have a positive test then you can get a referral and have diagnosis further refined at a specialty center." Furthermore, Hu adds, "Despite the number of spinal taps I do, it is never an appealing option to present to a patient. We need to refine the biomarkers in blood so that it is easily administered, even in primary care settings."

Ultrafast Optical Imaging, Microfluidic Technology Combine To Make Camera Capable of Detecting Rare CTCs in Blood

High-throughput image-based screening of rare cells is feasible, according to researchers from University of California Los Angeles (UCLA) in a proof-of-principle study published in *Proceedings of the National Academy of Science*s on July 17. The researchers say the analyzer is able to detect budding yeast and rare breast cancer cells spiked in blood and may be clinically applicable for early cancer detection and early assessment of therapeutic efficacy.

Conventional optical microscopy is limited in its ability to screen large populations of cells with high precision due to its low throughput and limited digital memory size. Flow-cytometry is also lacking in sensitivity to detect vary rare cell types. But the researchers say that their instrument has a throughput of 100,000 particles, which they believe they can improve, and a false positive rate of one in 1 million.

The STEAM flow analyzer, as it is called, is composed of three segments: a microfluidic device, the STEAM camera, and the real-time optoelectronic time-stretch image processor. Particles are first controlled to flow at a steady velocity and ordered by inertial lift forces in the microfluidic channel. The STEAM camera then takes images of the fast-flowing particles, and lastly, the real-time optoelectronic time-stretch image processor processes the images optically and electronically and performs automated particle screening in real time.

The device was capable of differentiating most white blood cells from the MCF7 breast cancer cell line in blood using a single molecular marker. The researchers say the STEAM system achieved real-time image-based screening with 75 percent sensitivity, one in 1 million specificity, and high statistical precision.

Lead author Keisuke Godal, a professor of physical chemistry at the University of Tokyo, says the technology can also be combined with a conventional cell sorter for further genetic analysis of the rare target cells. The group is currently working with clinicians at UCLA to begin validation trials using cancer patients' blood, Godal tells *DTTR*. He adds they are also planning on creating a library of circulating tumor cell images of various cancer types, which will be important for monitoring cancer metastasis.

Godal says it is premature to discuss concrete commercialization plans, but he plans on conducting the necessary clinical trials to work toward U.S. Food and Drug Administration approval in a few years. The instrument will cost about $250,000, "significantly cheaper than conventional medical imaging instruments (MRI, CT, PET)," he says. G2

Genetic Risk Predictors Identify Premalignant Oral Lesions Most Likely to Progress to Cancer

A group of molecular loss of heterozygosity markers are able to prospectively identify and risk stratify patients with premalignant oral lesions who are most likely to progress to oral cancer. The study, published in the September issue of *Cancer Prevention Research*, validated the results of a previous retrospective study and could improve patient therapeutic and prevention care strategies.

"The validation of the two risk models presented in this paper represents a significant first step in the evolution of a systematic decision-making process for this very heterogeneous group of lesions and an important move towards clinical application of these markers in a way that minimizes patient morbidity while maximizing health system and cost efficiency," write the study authors.

The researchers analyzed biopsy samples from 296 patients with mild or moderate oral dysplasia identified and followed over time by the British Columbia Oral Biopsy Service. In the initial model that utilized loss of heterozygosity at two loci (3p and/or 9p), patients classified as high-risk had an almost 23-fold increased risk for progression, compared to low-risk patients who retained heterozygosity. When the researchers incorporated two additional DNA molecular risk markers (loss of heterozygosity at loci 4q/17p) it further improved the risk prediction, with only 3.1 percent of low-risk patients progressing to cancer within five years, but 16.3 percent of intermediate-risk patients and 63.1 percent of high-risk patients having five-year cancer progression.

"That means that two out of every three high-risk cases are progressing," said study co-author Miriam Rosin, Ph.D., director, British Columbia Oral Cancer Prevention Program, in a statement. "Identifying which early lesions are more likely to progress may give clinicians a chance to intervene in high-risk cases, and may help to prevent unnecessary treatment in low-risk cases."

There are 300,000 new cases of oral cancers identified worldwide each year, with many of them preceded by premalignant lesions.

"These extraordinarily well-done and well-analyzed studies underscore the use of [loss of heterozygosity] in community-based risk assessment and, perhaps, in patient therapeutic and prevention stratification schemes," wrote Webster K. Cavenee, Ph.D., director of the Ludwig Institute for Cancer Research at University of California, San Diego, in an accompanying editorial. "As such, this represents a major advance for a decades old idea that has been waiting for such a test."

hsTroponin Algorithm Can Rule In or Out Heart Attack in an Hour

High-sensitivity cardiac troponin (hs-cTn) has improved early diagnosis of acute myocardial infarction (AMI), but the heightened sensitivity and lower positive predictive value of the newer assays has led to some clinical confusion. An algorithmic approach to interpreting hs-cTn can provide a definitive rule-in or rule-out diagnosis for 72 percent of patients in one hour, reducing the need for prolonged monitoring with serial blood sampling in the majority of patients, according to a study published online Aug. 13 in the *Archives of Internal Medicine*.

"Simple 'how-to-use' instructions for clinical decisionmaking are critically needed to take clinical advantage of the new assays and to shorten the time to rule-in and rule-out AMI," write the authors, led by Tobias Reichlin, M.D., from Brigham and Women's Hospital in Boston.

The researchers evaluated 872 patients with acute chest pain presenting to the emergency department. hs-cTn was measured both at presentation and after one hour.

Using a subset of these patients, an algorithm incorporating baseline values as well as absolute changes within the first hour was derived from 436 randomly selected patients and validated in the other half of the patients.

When applying the hs-cTn algorithm to the patients in the validation cohort, within one hour, 60 percent of patients could be classified as rule-out, 17 percent as rule-in, and 23 percent of patients as in the "observational zone." The rule-in algorithm had a baseline threshold of at least 60 ng/L or at least a 15-ng/L baseline to one-hour change threshold. The final rule-out algorithm had a baseline threshold of 12 ng/L or less and absolute change of 3 ng/L or less. The thresholds were not sensitive to sex, electrocardiogram features, or time from symptom onset. The hs-cTn algorithm achieved a sensitivity and negative predictive value of 100 percent for rule-out and a specificity of 97 percent and an 84 percent positive predictive for rule-in classification.

"Using this algorithm . . . may obviate the need for prolonged monitoring and serial blood sampling in three of four consecutive patients with acute chest pain," the authors conclude. "Compared with the six- to nine-hour window for a follow-up cTn test sample recommended in current guidelines, the shortening to a one-hour follow-up period would be substantial."

NIH to Fund $25 Million for Newborn Sequencing Pilots

The National Human Genome Research Institute (NHGRI) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development plan to award $25 million over five years to fund projects that will study "the implications, challenges, and opportunities" associated with the potential future use of genomic sequencing information in newborn screening. The projects funded under this cooperative agreement will explore both the analysis of genomic sequencing information as well as the ethical, legal, and social implications of this application.

While DNA-based testing has to date only been used for secondary confirmation of some disorders identified through primary newborn screening methodologies, NHGRI recognizes that advancements in sequencing technology combined with its continued drop in price "may make it possible to expand newborn screening in the future and substantially expand its clinical and public health value."

In the funding announcement NHGRI says the goal is for researchers to explore genomic sequencing for replicating or augmenting disorders currently tested under newborn screening as well as for expanding the scale of data available for analysis, including conditions not currently tested. All projects will also explore the ethical, legal, and social implications of sequencing. NHGRI applications are due Nov. 19 with projects expected to commence in July 2013.

"In five years we won't have the answers to all of the questions, but there will be important progress in a coordinated way. It is a valuable mechanism to jump-start the research," says Beth Tarini, M.D., an assistant professor of pediatrics at the University of Michigan in Ann Arbor, who will be applying for funding. "I am pleased that they incorporated ways to ethically and legally [explore newborn screening] to make it socially acceptable and palatable from a public policy perspective."

Concurrent with the release of NHGRI's funding announcement, the bioethics Hastings Institute (Garrison, N.Y.) released a report questioning whether prenatal human genome sequencing is a prudent clinical course to pursue, despite the fact that such analysis is feasible. The Hastings report says that the radical increase in scope of prenatal genetic data available from prenatal sequencing including poorly understood disease susceptibility information differs in ethically relevant ways from current prenatal genetic testing practice. Given that much of the potential data is of "questionable utility" and does not represent serious genetic conditions of high risk to fetuses and newborns, it highlights an inherent conflict of interests between parents' desire for information and potentially a child's desire to not know their genetic information.

The authors of the Hastings report, all from the Department of Bioethics at the National Institutes of Health, recommend that the medical community should offer guidance on which categories of information should be routinely offered to parents and that a child's right not to know his or her genetic information should not be breached unless the information is clearly useful for the parents or can improve health outcomes in the child.

Laboratory Tests Frequently Not Reviewed, Especially Those Ordered Day of Discharge

Laboratory tests requested early in an admission have a greater chance of being reviewed than those that are requested later in a patient's hospital stay, according to a study published online Aug. 13 in the *Archives of Internal Medicine*. More than 3 percent of all inpatient tests, including those with abnormal results, were not reviewed at discharge, representing both an opportunity to improve both patient care and test order optimization.

Researchers analyzed clinical pathology tests performed on inpatients in a 370-bed metropolitan teaching hospital. Test information was extracted from a computerized test-reporting system by inspecting electronic time stamps that were generated when the tests were viewed. Tests associated with deceased patients and tests communicated directly to the ordering physician were excluded.

Of nearly 663,000 individual laboratory tests performed over more than 6,700 inpatient admissions, nearly 38 percent of admissions had one or more results not read at discharge, with 1.5 percent of all tests remaining not reviewed two months following discharge. Tests ordered on the day of discharge, while only representing 7 percent of tests ordered, disproportionately contributed to the percentage of unread tests, accounting for about 47 percent of all tests not followed up on. Twenty-one percent of tests ordered on discharge day were not followed up compared with 1.8 percent of tests ordered on other days, highlighting an opportunity for laboratories or electronic ordering systems to optimize test ordering. Nearly 15 percent of all unreviewed tests at discharge had abnormal results, which may potentially affect the need for readmission.

"Hospital discharge is a critical transition point for many patients, with one in five patients experiencing an adverse event in the transition from hospital to home and with 62 percent of these adverse events being preventable. Failure to follow up test results after discharge contributes to this risk," write the authors led by Mei-Sing Ong, Ph.D., from Australian Institute of Health Innovations in Sydney.

G2 Insider

Implications of Within-Person Variability in hsCRP on Clinical Decisionmaking . . . Short-term, within-person variability in high-sensitivity C-reactive protein (hsCRP) measurements is significant enough to affect clinical decisionmaking, according to a study published online Sept. 3 in the *Archives of Internal Medicine*. The prevalence of patients clinically reclassified as a result of a subsequent test led the researchers to conclude that confirmatory testing may be called for in patients near cutoff points.

Based on evidence from clinical trials hsCRP has been recommended as an additional screening tool to assess cardiovascular risk in the general population and aid in clinical decisionmaking to begin statin therapy in patients with elevated low-density lipoprotein cholesterol concentrations. To better understand the implications of short-term variability in CRP on clinical practice, researchers from Johns Hopkins University analyzed data from 541 participants (16 to 69 years of age) who completed repeated examinations in the 2001-2002 National Health and Nutrition Examination Survey. Latex-enhanced nephelometry was used to measure hsCRP and an established cutoff point of a 10 mg/L was used to define an elevated CRP level (based on the American Heart Association and U.S. Centers for Disease Control and Prevention recommendations).

Participants were selected from the general population and had a mean age of 38 years, 50 percent were female, and 48 percent were white. The mean time between tests was 18.9 days with a mean hsCRP level at the first test of 4.5 mg/L and 4.3 mg/L at the second examination. Particularly at high values, the short-term within-person variability in CRP levels was significant, the authors report. Of patients with elevated hsCRP levels, approximately one-third of persons were reclassified as having normal CRP levels following repeat testing.

"Of note, we observed greater variation at higher values in cases in which clinicians are most likely to intervene," write the authors, led by Julie K. Bower, Ph.D. "Our results suggest that use of a single CRP measure for risk stratification may lead to substantial misclassification. Recommendations for repeated testing to confirm elevations in CRP level prior to altering medical decision-making may be warranted, particularly among those with CRP values near the risk cut points." G2

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