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DIAGNOSTIC TESTING & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

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INSIDE THIS ISSUE

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With New FDA Input, Momentum for LDT Regulation Accelerating

In what has been called a "critical milestone" towards enacting a comprehensive new oversight framework for diagnostic tests, the U.S. Food and Drug Administration (FDA) released its comments on the draft bipartisan bill crafted last year by Representatives Larry Bucshon (R-IN) and Diana DeGette (D-CO) on the House Energy and Commerce Committee.

While the Diagnostic Accuracy and Innovation Act (DAIA) was introduced back in March 2017, momentum seems to be building towards enactment of a new diagnostic oversight framework, possibly by the end of the year.

Continued on page 2

High-Sensitivity Troponin Test Rules Out Heart Attacks Faster

Use of a high-sensitivity cardiac troponin test (hs-cTnT) may be able to more quickly determine whether emergency department patients are having a heart attack, according to a research letter published in *Circulation*. The authors say that a new protocol for rapid rule-out of myocardial infarction using the hs-cTnT assay ruled out more than half of all patients within one hour.

Cardiac troponin is released into the bloodstream following damage to the heart. Traditional cTnT tests measure troponin levels at presentation to the emergency department and then three hours later. The rapid, hs-cTnT tests have been used in Europe for years, but are only entering clinical practice in the United States. There had been concern that adoption of hs-cTnT would result in an "unmanageable burden" of abnormal cardiac troponin results.

Researchers from University of Texas Southwestern Medical Center developed a novel hs-cTnT protocol, including the addition of a three-hour hs-cTnT measurement for patients classified as indeterminate at one hour. The proportion of patients eligible for early rule-out with the new protocol using hs-cTnT was compared to convention-

Continued on page 10

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With New FDA Input, Momentum for LDT Regulation Accelerating, *from page 1*

The draft bill, which was created with industry representation on the Diagnostic Test Working Group, established a new category of in vitro clinical tests (IVCTs) that includes both finished products (such as test kits), and lab test protocols (known as laboratory developed tests [LDTs]). In what can be seen as a compromise, the draft legislation included the creation of a new FDA center that would regulate test development and manufacturing, while lab operations would be overseen by the Centers for Medicare and Medicaid Services (CMS), which currently oversees CLIA-certified laboratories.

In early August, the FDA submitted 59 pages of comments on the DAIA. Reaction to the FDA's Technical Assistance (TA) document was strong and swift. The clinical laboratory industry renounced the agency's extensive comments as a dramatic departure from DAIA, with some calling it a rewrite of the bill, rather than a redlining. Representatives of the in vitro diagnostics industry, on the other hand, were pleased with the FDA's direction.

"We note that rather than providing technical amendments to [the bill], FDA has drafted a distinctly different framework," wrote the American Clinical Laboratory Association (ACLA) in comments to Congress. "ACLA recognizes that the FDA TA offers valuable insight into the priorities of FDA and certain concepts that could be incorporated into the Discussion Draft. However … ACLA believes that the framework set forth in the DAIA Discussion Draft should remain the starting point."

Despite lingering deep divisions within the diagnostics industry, some congressional staff members say that lawmakers are pushing for action on the bill by the end of the year, with the House Energy and Commerce Committee expected to meet this fall to consider comments in response DAIA.

The FDA Weighs In

"The FDA supports the goal of legislation to create a predictable path to market for all in vitro tests (IVCTs) that is a risk-based approach consistent with the least burdensome principle for regulation and assuring necessary safeguards for consumers," the agency wrote.

One area where the FDA has been praised was for its precertification program. For a number of tests, the agency has signaled that precertification could be a least burdensome regulatory pathway. The process the agency outlines parallels its approach to authorization for 23andMe's direct-to-consumer health risk tests. The agency wrote that for a group of tests using single technology or test method, or that have other shared elements (e.g., analytes, samples, purpose, intended population), the test developer would have to submit premarket review information for one test representative of the group of tests. Following precertification, the test developer could launch new tests that fall in that group without additional premarket review.

Despite praise for the precertification program, there were notable differences between the TA document and DAIA, which drew scrutiny from the clinical laboratory industry. A big difference includes narrowing of risk categories (DAIA allowed for a test to be characterized as low-, moderate-, or high-risk,

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> *"ACLA has repeatedly asserted, and continues to assert now, that LDTs are not devices, and therefore FDA has no authority with respect to LDTs under current law that would be 'retained' under any new framework."*
>
> — Julie Khani, President, ACLA

and outlines the varying regulatory requirements based on the test's risk level. However, the FDA dropped the moderate-risk category.) The FDA also eliminated calls for a strict review timeline in the draft bill and eliminated a new center for IVCTs, which it deemed unnecessary.

Industry Reaction

The FDA previously made clear that it believes increased regulation is needed as LDTs have become more complex, more broadly marketed, and increasingly risky to the patient and the public. Yet the clinical laboratory industry fundamentally questions the agency's authority to regulate laboratory activities, which are currently overseen by CMS.

"ACLA has repeatedly asserted, and continues to assert now, that LDTs are not devices, and therefore FDA has no authority with respect to LDTs under current law that would be 'retained' under any new framework," ACLA president Julie Khani wrote to Congress. She additionally stated that in addition to being "potentially duplicative and sometimes conflicting" with current CMS requirements, the FDA's device regulations would be "unnecessarily costly and burdensome" for labs.

ACLA raised many objections in its 26-page comments. Specifically, the organization called "unacceptable" the FDA's proposal that it can implement oversight provisions through guidance rather than regulation. ACLA said it bypasses "well-established notice-and-comment procedures, and fails to account for an economic impact analysis."

Furthermore, the association "strongly opposes" the FDA's revised definitions of analytical validity and clinical validity, speculating that the FDA intends to regulate IVCTs based on clinical utility. ACLA also objects to the FDA's transition provisions and grandfathering provisions that could enable the FDA to "claw back" grandfathered tests "at its discretion without basis in meaningful standards."

In comments to Congress, Pew Charitable Trust AdvaMedDx, which represents in vitro diagnostic tests, expressed support for FDA oversight of "all diagnostics" using a risk-based approach.

Takeaway: With lawmakers and some industry groups pushing for resolution by the end of the year, comprehensive diagnostic reform may soon become a reality. However, stakeholders and lawmakers must reconcile the notable differences between the FDA's comments and the existing draft legislation.

Be a part of the conversation this year!

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Hidden Blood in Stool May Indicate Higher All-Cause Death Risk

"Invisible" blood in stool may predict death from a wide range of causes, not just colorectal cancer, according to a study published July 16 in *Gut*. A positive fecal occult blood test (FOBT) increases all-cause mortality risk, including circulatory, respiratory, neuropsychological, and non-colorectal cancers, by 58 percent.Despite development of new drugs, medications still fail to control seizures in 20 percent to 30 percent of patients. Drug selection remains largely a function of trial and error. Furthermore, drug-resistant epilepsy accounts for the vast majority—estimated to be nearly 80 percent—of the cost of all epilepsy treatment.

"If the eye is the window to the soul, is a fecal test the window to general health?"

— Uri Ladabaum

Testing for the presence of hemoglobin in stool is a widely used tool for colorectal cancer screening, including in the population-based colorectal cancer screening program in Scotland, the Scottish Bowel Screening Programme, that uses mailed test kits for a guaiac FOBT (Immunostics; Ocean, New Jersey, USA).

The researchers analyzed results for all individuals who participated in gFOBT screening in Tayside, Scotland through either a pilot period (March 2000 to September 2007) or the subsequent full program implementation (2007 onwards). Patients were between the ages of 50 and 69 years for the pilot, and up to 74 years during the full program. Test result (positive or negative) were linked with mortality data from the National Records of Scotland database, with follow-up through March 2016.

Based upon the 133,921 patients included in the analysis, positive test results were seen in 2.0 percent of the cohort. As would be expected, those with a positive gFOBT test result had higher mortality. But these results extended beyond colorectal cancer and were seen for all-cause mortality, including circulatory disease, respiratory disease, digestive diseases (excluding colorectal cancer), neuropsychological disease, blood and endocrine disease, and non-colorectal cancers. These findings remained even when adjusting for gender, age, socioeconomic status, and medications, like aspirin, that can cause bleeding.

"It would appear that the association between hemoglobin in feces and premature non-colorectal cancer death cannot be explained simply by its association with obvious confounding factors," write the authors led by Gillian Libby, from Ninewells Hospital in Scotland. With further validation, the authors suggest "a positive test result could be used alert invitees to the risk of reversible non-communicable disease regardless of the presence or absence of colorectal neoplasia."

The authors caution that since gFOBT are qualitative tests the effect of an incremental increase in fecal hemoglobin concentration could not pinpointed. However, they explain that gFBOT usually become positive at a concentration of around 80 µg hemoglobin/gram feces, which would be the "high end" of the fecal hemoglobin spectrum that would be expected in a population.

"If the eye is the window to the soul, is a fecal test the window to general health?" asks Uri Ladabaum, from Stanford University in California, an accompanying

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commentary. "Perhaps more importantly, if occult blood in feces is a predictor of life expectancy and multiple [non-bowel cancer] causes of death, the inevitable next questions concern the implications for organized [bowel cancer] screening programs or opportunistic [bowel cancer] screening."

Takeaway: Positive FOBT tests may indicate a health risk beyond colorectal cancer.

Preimplantation Genetic Testing Improves IVF Outcomes

Preimplantation genetic testing for aneuploidy (PGT-A) can mitigate the negative effects of maternal age on in vitro fertilization (IVF) outcomes by selecting normal embryos that are more likely to lead to sustained implantation, according to a study published in the July issue of *Fertility and Sterility*.

The researchers found that aneuploidy was detected in 42.9 percent of blastocysts from nondonor cycles.

"Our findings provide evidence that successful IVF outcomes can be achieved without multiple-embryo transfer when transfers are combined with the use of single nucleotide polymorphism-based PGT-A," write the authors led by Alexander Simon, from Natera in San Carlos, Calif. "We hope that these findings will allay both patient anxiety about the possibility of miscarrying a single transferred embryo (i.e., without a "backup") and physician concern about reduced pregnancy rates."

IVF outcomes remain low, with fewer than half of all transferred embryos leading to a successful pregnancy in the United States. Aneuploidy—embryos with an abnormal number of chromosomes—is the leading cause of failed IVF. It is hoped that PGT-A can improve IVF outcomes, but data has been limited to date.

In what is thought to be the largest study of pregnancy outcomes in women undergoing IVF guided by the use of single nucleotide polymorphism- (SNP-) based PGT-A, researches evaluated outcomes in 974 women (aged 20 to 46 years) undergoing IVF treatment (1,883 IVF cycles from Oct.1, 2010, to Aug. 31, 2013) at Pacific Fertility Center (PFC; San Francisco, Calif.) and Conceptions Reproductive Associates of Colorado (CRA; Litteton). Elective PGT-A was performed using a 24-chromsome SNP assay (Spectrum PGT-A; Natera) on three to eight trophectoderm cells from high- and medium-grade embryos on culture day 5 or 6. Biopsy samples were processed and shipped overnight to Natera's CLIA-certified lab.

Overall, 53 percent of IVF cycles were tested with PGT-A. Interesting, PGT-A uptake differed by site, with CRA performing PGT-A on 81.3 percent of cycles (881 of 1,084) versus 40.5 percent at PFC (1,002 of 2,470).

The researchers found that aneuploidy was detected in 42.9 percent of blastocysts from nondonor cycles. The proportion of aneuploid blastocysts increased with maternal age, from 26.9 percent in women younger than 35 years of age to more than 70 percent in women over 40 years of age.

Using PGT-A-guided embryo selection, the fertility clinics observed an implantation rate of 69.9 percent, clinical pregnancy rate per transfer of 70.6

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percent, and live birth rate per transfer of 64.5 percent in 1,621 nondonor frozen cycles. In addition, PGT-A-related outcomes remained relatively constant across all maternal ages. There were no statistically significant differences in pregnancy outcomes for single-embryo transfers versus double-embryo transfers using PGT-A-selected embryos.

"[The] rapid increase in aneuploidy and decrease in the probability of obtaining euploid embryos after the age of 35 years, underscore the importance of accurate identification and selective transfer of euploid embryos in women of advanced maternal age undergoing IVF treatment," writes Simon and colleagues.

Takeaway: PGT-A-guided embryo selection improves IVF outcomes, even in women with advanced age and using single-embryo transfers.

Targeted Sequencing Panel May Aid Diagnosis of Movement Disorders

A high-coverage sequencing panel is a useful and efficient means to identify genes associated with movement disorders, according to a study published online June 18 in *JAMA Neurology*. The authors say the panel was a cost-effective diagnostic alternative to whole-exome and whole-genome sequencing (WES and WGS).

Movement disorders, including Parkinson's disease, are known for their marked heterogeneity in genotype and phenotype, which complicate diagnosis. The authors say that molecular diagnosis by standard Sanger sequencing is "tedious, time consuming, and inefficient," plus analyses of the known implicated genes are not yet always routinely available. Further, they say that that variants of unknown significance (VUS) uncovered using WES and WGS can complicate return of results.

So, the French researchers developed a targeted sequencing approach using a panel of 127 genes involved in movement disorders and evaluated its performance in a cohort of 378 patients seen at tertiary movement disorder clinics (September 2014 to July 2016). Patients had at least one chronic movement disorder and had an age at onset younger than 40 years and/or a family history of movement disorders (37 percent). Patients were classified as parkinsonism, dystonia, chorea, paroxysmal movement disorder, and myoclonus. Twenty-three patients suspected of having inherited cerebellar ataxia underwent WES. Using a Hiseq 4000 Sequencing System (Illumina) the researchers achieved a mean depth of coverage of 1266 × with a mean of 99.7% of targeted regions well covered in each patient (× >30).

The diagnostic yield was 22 percent and uncovered 49 novel pathogenic variants. Patients diagnosed with pathogenic variants were significantly younger versus patients without diagnosis (median age, 27 versus 35 years). Diagnostic yield was also significantly lower in patients with dystonia versus the overall cohort and the parkinsonism group.

The 49 novel probable pathogenic variants were identified most commonly in PARKIN, GBA, and LRRK2 genes. A total of 74 VUS were identified in 60

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"The high depth of coverage and the smaller portion of poorly covered regions achieved with our strategy ensure a high sensitivity and specificity of detecting pathogenic events in the regions of interest and enable the identification of single-nucleotide variants, indels, but also copy number variants, which remain a challenge in next-generation sequencing."

— Solveig Montaut, M.D.

other patients. WES analysis of the cohort of 23 patients with cerebellar ataxia had an overall diagnostic yield of 26 percent, similar to panel analysis; however, the cost was much greater.

"The high depth of coverage and the smaller portion of poorly covered regions achieved with our strategy ensure a high sensitivity and specificity of detecting pathogenic events in the regions of interest and enable the identification of single-nucleotide variants, indels, but also copy number variants, which remain a challenge in next-generation sequencing," write the authors led by Solveig Montaut, M.D., from Hôpitaux Universitaires de Strasbourg in France.

The estimated cost of the gene panel strategy without labor costs was $156 per patient ($70 for reagents cost, $68 for run cost, and $18 for consumable items). For the WES cohort, the cost was between $850 and $1,113 per patient without labor costs. To complete the gene panel strategy for a series of 24 patients turnaround time varied between 2 to 3 full days, while data analysis of a series of six exomes required 7 to 10 days.

Takeaway: Targeted sequencing strategies may be more effective for diagnosis of movement disorders.

Parkinson's Biomarkers Needed

Biomarkers for Parkinson's disease are urgently needed, according to a perspective piece published Aug. 15 in *Science Translational Medicine*.

Parkinson's is the second most common neurodegenerative disorder, affecting more than 4 million people worldwide. These numbers, experts say, are projected to double in the next few decades. Yet, the pipeline of disease-modifying therapies is "meager," say experts from 36 organizations.

The experts, representing government, academia, and nonprofit funding agencies are calling for collaboration and a new strategy to discover these critical biomarkers.

As with other biomarkers intended for clinical purposes, the panel says potential biomarkers should have a reasonable effect size alone or in combination and must demonstrate clear reproducibility across patient cohorts. Practically, the experts say, assays should take into consideration the cost and complexity to detect biomarkers and the capability for frequent or serial testing.

The group says that previous research efforts have largely focused on biomarkers that distinguish Parkinson's disease from healthy individuals or those with other neurodegenerative diseases, but the authors call for a shift to focus on biomarkers that differentiate within Parkinson's disease itself, as their disease manifestations can be heterogeneous in patients.

"Creation of tools enabling development of disease-modifying therapies in Parkinson's disease is a reachable, immediate goal, worthy of research investment," write the authors led by Alice S. Chen-Plotkin, from University of Pennsylvania in Philadelphia.

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SPECIAL FOCUS: Lung Cancer

New Test Aids Lung Cancer Risk Assessment, But Survival Benefit of Comprehensive Sequencing Questioned

Lung cancer-related testing is receiving a lot of attention, but recent results appear to show mixed benefits for these emerging tests.

There is an urgent need to improve lung cancer risk assessment, as current screening strategies miss a large proportion of new cases. A recent small study that used protein-based biomarkers to enhance risk-based screening stratification shows promise.

However, a separate study shows that comprehensive sequencing is penetrating community-based care for lung cancer, yet the effusion of technology is not accompanied by any simultaneous survival benefit, suggesting that the technology adoption has outpaced the utility of results.

"The biomarker panel more accurately identifies at-risk smokers who should proceed to screening, even if they're not at the highest risk based on smoking history alone."

— Samir M. Hanash, M.D., Ph.D.

Biomarkers Improve Lung Cancer Risk Assessment

Biomarker-based risk profiling has the potential to better identify at-risk patients for lung cancer screening, according to a brief report published July 12 in *JAMA Oncology*. The proof-of-principle study shows that four protein biomarkers outperform traditional risk prediction models based on smoking history.

"The biomarker panel more accurately identifies at-risk smokers who should proceed to screening, even if they're not at the highest risk based on smoking history alone," said lead author Samir M. Hanash, M.D., Ph.D., University of Texas MD Anderson Cancer Center in Houston, in a statement. "A positive blood test means an ever-smoker is as much, if not more so, at risk of having lung cancer as a heavy smoker with a low biomarker score."

Current U.S. Preventive Services Task Force recommendations call for low-dose computed tomography-based screening for individuals aged 55 to 80 years who have smoked 30 pack-years. Yet, this protocol entirely misses non-smokers who go on to develop lung cancer.

Researchers from the Integrative Analysis of Lung Cancer Etiology and Risk (INTEGRAL) Consortium for Early Detection of Lung Cancer developed a biomarker risk score based on prediagnostic samples from lung cancer patients. The biomarker score is based on four blood-based protein markers—cancer antigen 125, carcinoembryonic antigen, cytokeratin-19 fragment, and the precursor form of surfactant protein B. The biomarker score, integrated into the smoking-based prediction model, was then validated in a cohort of 63 ever-smoking patients with lung cancer and 90 matched controls.

The researchers found that the integrated risk prediction model significantly outperformed the smoking only-based prediction mode. It had superior sensi-

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SPECIAL FOCUS: Lung Cancer

tivity—identification of smokers who later developed lung cancer—without increasing the number of false-positives.

Twenty-six of the 62 incident lung cancer cases in the validation study qualified for LDCT screening according to USPSTF criteria. The biomarker-based risk prediction model, 40 cases would have been identified. Furthermore, the authors say, the biomarker score could have reduced screening of individuals not destined to develop lung cancer from 15 to four, without affecting the assessment of future lung cancer cases.

"Our findings also indicated that the improvement in discrimination afforded by the biomarker score is more modest beyond the initial year after blood draw, which suggests that an annual biomarker test may be necessary in a screening program," wrote Hanash and colleagues.

Broad-Based Sequencing Does Not Improve Survival

Broad-based genomic sequencing does not improve survival over routine EGFR and/or ALK testing among patients with advanced non-small cell lung cancer (NSCLC) receiving treatment in the community setting, according to a study published Aug. 7 in the *Journal of the American Medical Association*. Among those that received broad-based genomic sequencing results informed treatment for a non-EGFR mutation or ALK rearrangement in fewer than 5 percent of patients, raising questions about results' actionability.

Testing for EGFR and ALK alterations in now standard of care for patients with advanced NSCLC due to the established survival benefit afforded by targeted treatments. However, some recommendations, like those from the National Comprehensive Cancer Network, call for testing using broad-based genomic sequencing to identify rare driver mutations and to facilitate clinical trial eligibility for possible emerging targeted treatments. Yet there is limited evidence to date to evaluate whether broad-based genomic sequencing meaningfully uncovers clinically actionable mutations, affects patient outcomes, and or is cost-effective.

A large study compared the impact of broad-based genomic sequencing versus routine testing (EGFR mutations and/or ALK rearrangements) for 5,688 NSCLC patients treated in the community setting (191 practices; (Jan. 1, 2011, through July 31, 2016) may not currently offer a survival advantage

The researchers found that 15.4 percent of patients in the community setting received broad-based genomic sequencing. All patients received EGFR testing, while 95 percent received ALK testing.

Among the 875 patients who received broad-based genomic sequencing, the vast majority (88.9 percent) had a genetic mutation identified. There were 247 unique genetic mutations identified, including most commonly TP53 (55.1 percent), KRAS (34.2 percent), EGFR (21.9 percent), CDKN2A (15.7 percent), and STK11 (12.2 percent). Other than EGFR and ALK, the most common actionable

Continued on page 10

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SPECIAL FOCUS: Lung Cancer

alterations detected with broad-based genomic sequencing—those for which patients received targeted treatment—were BRAFV600E, MET, and ERBB2.

Of those receiving broad-based sequencing, 4.5 percent received targeted treatment based on testing results, 9.8 percent received routine EGFR/ALK targeted treatment, and 85.1 percent received no targeted treatment. Patients receiving broad-based genomic sequencing were more likely to receive immunotherapy (4.0 percent), even though sequencing is not needed to initiate immunotherapy. Additionally, significantly more patients receiving broad-based sequencing enrolled in clinical trial regimens versus patients receiving routine testing. There were no significant associations between broad-based genomic sequencing and either overall survival or 12-month mortality versus routine testing.

"There is limited availability of targeted treatments that are both effective and have minimal toxicity to target an ever-expanding list of tumor mutations," write the authors led by Carolyn Presley, M.D., from Ohio State University in Columbus. "This study highlights how broad-based genomic sequencing has disseminated beyond traditional research settings ahead of a demonstrated association with better survival."

Takeaway: Biomarkers may enhance risk-based screening strategies. But, comprehensive sequencing of advanced NSCLC cases fails to show a survival benefit. Emerging lung cancer tests will benefit from further validation and cost analysis.

High-Sensitivity Troponin Test Rules Out Heart Attacks Faster, *from page 1*

al fourth-generation, three-hour cTnT assays. cTnT and hs-cTnT were measured at 0, 1, and 3 hours after presentation in 536 patients with symptoms suggestive of MI (August to October 2017).

Based on hs-cTnT results, individuals were classified into two categories, "ruled out" or "abnormal." Using the conventional assay, patients were ruled out if cTnT was <0.01 ng/mL at all time points and abnormal if any value was ≥ 0.01 ng/mL. Three cardiologists adjudicated final diagnosis based on all available clinical information.

Using the conventional assay, the researchers ruled out 80.4 percent of patients at three hours. Using the new hs-cTnT protocol, 83.8 percent ruled out by 3 hours, including 30.0 percent at baseline, 24.8 percent at 1 hour, and 28.9 percent at 3 hours. Significantly fewer patients were classified as abnormal using the new protocol versus the conventional assay (16.2 percent versus 19.6 percent). The new protocol had a sensitivity and negative predictive value of 100 percent, specificity of 86 percent, and positive predictive value of 13 percent for a final adjudicated diagnosis of MI. Among patients who ruled out, there were no recurrent MI events reported over 30 days of follow-up.

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Three hs-cTnT assays have received clearance from the U.S. Food and Drug Administration.

- **January 2017:** Roche's Elecsys Troponin T Gen 5 Stat blood test for use on cobas analyzers.
- **July 2018:** Siemens Healthineers' high-sensitivity troponin I assays for the Atellica IM and ADVIA Centaur XP/XPT in vitro diagnostic analyzers.
- **June 2018:** Beckman Coulter Diagnostics' Access hsTnI, for use on the Access 2, DxI, and the Access family of immunoassay systems.

"The positive predictive value of an abnormal hs-cTnT value was notably lower in this population than in prior studies, reflecting similar specificity applied to a population with much lower MI prevalence," write the authors led by Rebecca Vigen, M.D., from University of Texas Southwestern Medical Center in Dallas. "Thus, clinical judgment remains essential in the interpretation of abnormal troponin values as the hs- cTnT assay becomes adopted in the United States, where troponin is measured more indiscriminately than in many other countries."

Takeaway: hs-cTnT can rule out heart attacks faster in the emergency department than conventional assays, seemingly allaying concerns of a larger burden of abnormal results. This next generation of sensitive tests appears poised for clinical adoption in the United States.

HBA1c Blood Test May ID Gestational Diabetes Risk in First Trimester

First trimester HbA1c may aid in early identification of at women at risk of gestational diabetes (GD), according to a study published in Scientific Reports. Such early screening could allow for lifestyle interventions before the condition develops and adverse pregnancy outcomes can occur.

HbA1c is most commonly used to diagnose type 2 diabetes among adults. It is also used among high-risk women at the first prenatal visit to identify women with overt type 2 diabetes, but it is not currently used to screen for GD. Furthermore, little is known about the normal ranges for HbA1c across pregnancy.

The researchers from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) conducted a nested GD case-control study among participants in the NICHD Fetal Growth Studies-Singleton Cohort (2009 to 2013).

HbA1c was assessed in 107 GD cases and 214 controls matched based upon maternal age, race/ethnicity, and gestational week of blood collection. Blood collection occurred at 8–13, 16–22, 24–29, and 34–37 gestational weeks. Women with HbA1c ≥ 6.5% at enrollment or who had a hemoglobin variant were excluded.

The researchers found that women who later developed GD had significantly higher HbA1c at 8–13 gestational weeks. This difference remained significant throughout pregnancy. For each 0.1% HbA1c increase at 8–13 weeks there was an adjusted 22 percent increased risk of GD risk. Additionally, first trimester HbA1c significantly improved GD prediction over conventional risk factors, like age, race/ethnicity, pre-pregnancy overweight and

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> *"The low sensitivity at higher HbA1c levels suggests that HbA1c may not be a good substitute for a second trimester oral glucose tolerance test, which tests the acute response to the glucose challenge and how women respond to the increased insulin resistant environment of late pregnancy."*
>
> — Stefanie Hinkle

obesity, family history of diabetes, and GD in a prior pregnancy.

There was suggestion that the optimal HbA1c cut-point was at (95% CI 62%, 88%).

At an HbA1c of 5.7% (similar to type 2 diabetes outside of pregnancy), the sensitivity was 21 percent and the specificity was 95 percent. However, with a cutoff point of 5.1%, sensitivity was 47 percent and the specificity was 79 percent.

"The low sensitivity at higher HbA1c levels suggests that HbA1c may not be a good substitute for a second trimester oral glucose tolerance test, which tests the acute response to the glucose challenge and how women respond to the increased insulin resistant environment of late pregnancy," write the authors led by Stefanie Hinkle, from NICHD in Bethesda, Md. "However, more importantly, the high specificity at 5.7% (39 mmol/mol) suggests that with this threshold few low-risk women, who otherwise would not receive early screening, would be incorrectly diagnosed by an elevated first trimester HbA1c level."

Takeaway: Use of HBA1c testing early in pregnancy may identify women at risk for GD before complications occur.

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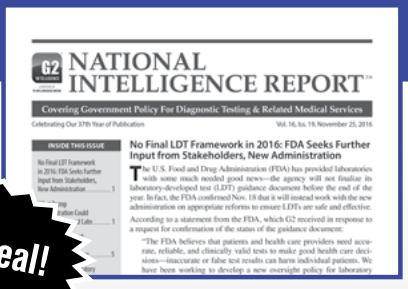
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