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New Trends, Applications, and IVD Industry Analysis

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Labs Can Provide Novel Support for Physicians Ordering Multigene Panels

As the price of sequencing continues to drop and genomic testing in oncology continues to shift towards larger panels, physicians have self-reported difficulty in understanding results. Yet, the success of personalized medicine is dependent upon physicians' ability to understand and act upon genomic results.

Two studies presented in poster sessions at the American Society of Clinical Oncology annual meeting (Chicago; June 1-5) highlight how laboratories can play an important and expanded role in making

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C-reactive Protein May Inform Antidepressant Medication Selection

Baseline C-reactive protein (CRP) levels may be informative to guide treatment selection and improve clinical outcomes for outpatients being treated for depression, according to a study published in the April issue of *Psychoneuroendocrinology*. In this trial, CRP was the only inflammatory biomarker to predict clinically meaningful treatment outcomes..

Traditionally, antidepressant selection has been based on subjective factors such as cost or patients and/or provider preferences. This trial-and-error approach often requires multiple attempts to achieve adequate symptom control.

The present study involved secondary data analysis of a subset of participants in the Combining Medications to Enhance Depression Outcomes trial. Participants had been randomly assigned to either SSRI monotherapy (n = 51) or bupropion-SSRI combination (n = 55). A predefined CRP threshold of 1 mg/L was used to assess baseline plasma samples. In addition to CRP, serum amyloid P component, and alpha-2-macroglobulin were measured using the Bioplex Pro human-acute-phase 4-plex panel. Depression severity and side effects were the treatment outcomes evaluated weekly or every other week over the 12-week acute phase.

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tumor panel results more understandable—either through consultation or changing the format of the reports themselves.

Remote Genomic Consultation

Remote genomic consultation can be effective in supporting community-based oncologists' use of multigene genomic tumor panels, found researchers from Fox Chase Cancer Center in Philadelphia.

"Early multigene genomic tumor panel uptake has been slow among community oncologists due to their lower confidence to order, interpret, and act upon results," writes lead author Michael J. Hall. To address this the researchers evaluated the effectiveness of telephone-based genomic consultation between community oncologists (in four practices) and an academic clinician linked to an institutional genomic tumor board.

The nine community oncologists completed baseline and follow-up assessments. Tumor blocks were evaluated at Fox Chase Cancer Center using a 50-gene tumor panel. Panel results were presented, when warranted, to the genomic tumor board. A tailored summary was provided to community oncologists.

The researchers found that 12 percent of samples were inadequate. Of the remaining samples tested, the researchers found that all yielded at more than one variant (range one to six). The majority of patients (59 percent) had a clinically relevant variant. Six variants were potentially actionable with approved therapy, while three other variants were associated with therapies in Phase I/II trials.

At baseline, the nine community-based oncologists had limited experience with tumor panels, with three-quarters of them having ordered less than five panels. Community oncologists' self-reported barriers for panel testing included poor understanding of multigene tumor panels (67 percent), cost (89 percent), uncertain benefit (44 percent), and poor access to targeted therapies (67 percent). At follow up, half of community oncologists found genomic consultation "very useful." Nearly two-thirds that multigene tumor panels paired with genomic consultation would "probably/definitely" increase their use of the panels.

Interactive Genomic Reports

Interactive, genomic reports may improve physicians' ability to accurately assess genomic data, according to a study presented by researchers from the City of Hope in Duarte, Calif.

The researchers created web-based, interactive reports with enhanced data visualization elements and embedded decision support for panels with more than 300 genes. The study involved vignette-based surveys to determine whether exposure to the interactive reports, as compared to static reports, improves physicians' genomic understanding and report-based satisfaction. More than 100 physicians at a major cancer center participated.

The researchers found that prior to viewing the case-based vignette reports, just over one-third of physicians reported that they found it difficult to make

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treatment recommendations based on the standard report in their routine practice. After viewing the case-based vignettes, physicians' overall comprehension scores did not increase significantly. However, physicians who viewed the interactive report were significantly more likely to correctly assess sequencing quality and understand when reports needed to be interpreted with caution (e.g., low tumor purity). Satisfaction scores were significantly higher in the interactive group, compared to the static group.

The majority of physicians (88 percent) physicians confirmed the need for additional genomic support for providers. Of these physicians, two-thirds reported that interactive genomic reports would provide helpful support.

Takeaway: There are many novel ways (including remote consultation and enhanced reports) that laboratories can support physicians increase their understanding of results from multigene tumor panels.

POC HCV RNA Testing Key to Achieving National Viral Elimination Goals

The Xpert HCV Viral Load test (Cepheid, Sunnyvale, Calif.) for hepatitis C virus (HCV) has good accuracy for detecting viral RNA using whole blood from a finger stick, according to a study published in the July issue of *The Lancet Gastroenterology & Hepatology*. The authors say this is the first published evaluation of an assay for HCV RNA detection using finger-stick whole-blood collection in a clinical setting and is an important step towards enabling point-of-care (POC), HCV RNA testing, particularly in high-risk settings.

> *"Sensitive HCV RNA testing of whole blood collected by finger-stick is particularly appropriate for populations with a high prevalence of HCV infection."*
>
> — Jason Grebely, Ph.D.

The lack of validated POC tests is a known challenge to improving HCV diagnosis and linkage to treatment. POC HCV RNA testing offers a two-fold advantage over antibody testing in that it an enable diagnosis of active infection (versus previous exposure with antibody testing) and they can do so in a single visit.

"Sensitive HCV RNA testing of whole blood collected by finger-stick is particularly appropriate for populations with a high prevalence of HCV infection," write the authors led by Jason Grebely, Ph.D., from the Kirby Institute in Australia. "First, people who inject drugs often have poor venous access as a result of injecting, making the collection of blood via venepuncture very difficult … Second, data have shown that on-site HCV testing with integrated care improves linkage to HCV care."

The Lancet study evaluated testing conducted on 210 participants at five sites with high-risk populations (drug and homeless service programs). The study compared the performance of the Xpert HCV Viral Load test for HCV RNA detection using both venepuncture and finger-stick collection to the Abbott RealTime HCV Viral Load assay (gold standard).

Final analysis included data from the 150 participants that had viral load testing results for all three assays tested. Sensitivity of the Xpert HCV Viral Load assay for HCV RNA detection in plasma collected by venipuncture was 100% and specificity was 99%. Sensitivity of the assay for HCV RNA detection in

samples collected by finger-stick was 95.5% and specificity was 98.1%. The authors say that one percent of samples tested did not provide a result on the Xpert HCV Viral Load assay because of low sample volume in the cartridge.

"The manufacturer of the assay is using this study to optimize the assay so that the results of the assay will be provided in 60 minutes, which should lead to the development of a commercially available Xpert HCV Viral Load test for HCV RNA detection in capillary whole blood collected by finger-stick," writes Gebely and colleagues.

Takeaway: This first validation of a POC HCV RNA test is an important step to increasing one-step testing and linkage to care, particularly for high-risk populations, and achieving a national screening strategy.

New Diagnostics to Play Role in National HCV Elimination Strategy

Development of new rapid, POC diagnostics has an important role to play, according to a report, *A National Strategy for the Elimination of Hepatitis B and C*, released by the National Academies of Sciences, Engineering, and Medicine.

The National Academies convened an expert committee to describe a strategy for eliminating viral hepatitis as a U.S. public health problem by 2030. The first report concluded that both hepatitis B and C could be eliminated as public health problems. The second report, released in March, recommends a plan to do so.

The diagnostics-related recommendations made by the expert committee include:

- The U.S. Centers for Disease Control and Prevention (CDC) should work with states to identify settings appropriate for enhanced viral hepatitis testing based on expected prevalence.
- People in jails and prisons are known to have a particularly high burden of viral hepatitis and correctional facilities provide an opportune place to conduct testing.
- CDC should work with the National Cancer Institute to attach viral etiology to reports of liver cancer in its periodic national reports on cancer.
- The National Committee for Quality Assurance should establish measures to monitor compliance with viral hepatitis screening guidelines and include the new measures in the Healthcare Effectiveness Data and Information Set quality measures.

Publications Validate LDT for Sperm Function, as Measure of Fertility

The Cap-Score Sperm Function Test (Androvia LifeSciences) can accurately assess sperms' capaciatation state, a necessary condition for male fertility, and report the percentage of sperm in a sample that can actually fertilize an egg. The company, which published two papers—clinical and technology validation studies—April 18 in *Molecular Reproduction and Development*, says the test holds clinical value as a general screening test for men uncertain about their fertility.

Approximately 40 percent of infertility is attributable to male factors. Yet, standard semen analysis, which assesses sperm count, motility, and morphology, yields a diagnosis in less than 50 percent of male infertility cases. The rest of infertility cases are believed to be caused by failings in sperm function, which cannot be measured by traditional semen analysis. Experts say that a test that could measure sperm function—a sperm's ability to fertilize—would have huge clinical importance.

"A simple diagnostic assay would provide a needed functional complement to the descriptive assessments of traditional semen evaluations," writes lead author Melissa Moody, from Androvia LifeSciences (Mountainside, N.J.) in one of the papers. "Identifying sperm with deficiencies in fertilizing ability will allow for a more specific understanding of what is now categorized as 'idiopathic infertility.' Of much greater practical importance, such a physiological assessment would enable a clinician to effectively counsel a couple toward the most appropriate form of assisted reproduction to achieve pregnancy."

The Cap-Score is an in vitro, laboratory-developed test designed to assess sperm function, by measuring capacitation. The test involves incubating sperm in non-capacitating medium, as well as medium containing capacitating stimuli. The score measures response to the capacitation stimuli by measuring monosialotetrahexosylganglioside (GM1) localization patterns, responsible for capacitation. The test result—the Cap-Score—reports the proportion of sperm within a sample that display the localization patterns associated with capacitation, compared to a normal, fertile population.

One of the two published papers validated the accuracy, reproducibility, and precision of the Cap-Score test. The second paper assessed the clinical utility of the Cap-Score assay in two clinical trials. Together, these findings showed that capacitation status strongly correlated with a man's history of fertility.

In the first study involving men with long histories of unexplained infertility pursuing assisted reproduction in a tertiary care fertility clinic, men with high Cap-Scores (above a 39.5 percent threshold) had a 92 percent chance of conceiving by natural conception or within three cycles of intrauterine insemination. In contrast, men with Cap-Scores below the 39.5 percent threshold had only a 21 percent chance of conceiving. In the second trial, the Cap-Scores from a group of 76 men with proven fertility were compared against those of 122 men seeking semen analysis because of difficulty conceiving. A significantly higher percentage of men questioning their fertility (34 percent) had abnormally low Cap-Scores, compared with only 13 percent of the known fertile men.

A previous study by the company suggested that use of the Cap-Score to personalize management of couples with unexplained infertility projected to result in higher clinical pregnancy rates and reduced medical costs (nearly $5,000) in couples with women 35 to 37 years of age, compared to the current standard of care.

Takeaway: Results from clinical and technology validation studies of the Cap-Score Sperm Function Test suggest the utility of the test, in conjunction with standard semen analysis, for screening males with suspected infertility.

Sequencing-Based Screening Needed for Therapeutic Stem Cells

One of the potential therapeutic advantages of stem cells is that they can regenerate. But, a new study, published May 11 in *Nature*, suggests that the longer stem cell lines replicate the more cancer-related mutations they acquire, leading the authors to recommend that stem cells and therapies derived from them undergo "careful" genetic characterization before clinical use.

The study found that approximately 5 percent of stem cell lines analyzed developed mutations in p53, a tumor-suppressing gene, responsible for controlling cell growth and division. The authors say that stem-cell based therapies should still be investigated, but that genetic sequencing technologies should be used to screen for mutated cells in stem cell cultures. Without such screening, stem cell transplants could contain an elevated cancer risk.

"Our analyses indicate that researchers have unknowingly and routinely used [stem] cells that harbor cancer-related missense mutations in TP53," write the authors led by Florian Merkle, Ph.D., from Harvard University. "These findings have practical implications for the use of human embryonic stem cells in disease modeling and transplantation medicine."

The researchers sequenced the exomes of 140 independent human embryonic stem cell lines listed on the National Institutes of Health registry, which included 26 lines developed for potential clinical use.

Sequencing revealed that five unrelated cell lines carried six mutations in the TP53 gene. The TP53 mutations were the dominant negative mutations commonly seen in human cancers. The researchers also found that the fraction of TP53 mutant alleles increased with passage number under standard culture conditions, suggesting, the authors say, that the mutation may offer a growth advantage to stem cells in culture.

"Our findings indicate that an additional series of quality control checks should be implemented during the production of stem cells and their downstream use in developing therapies," said coauthor Kevin Eggan, Ph.D., from Harvard University. "Fortunately, these genetic checks can be readily performed with precise, sensitive, and increasingly inexpensive sequencing methods."

Takeaway: Stem cells acquire potentially harmful p53 mutations, which should be screened for before transplantation or use for other therapeutic purposes.

Push-Alerts of Lab Results Speeds Discharge from Emergency Dept.

Smartphone push-alert notification of troponin laboratory results allow physicians to discharge patients seen in the emergency department for chest pain sooner, compared to physicians who do not receive push alerts, according to a study published online May 9 in the *Annals of Emergency Medicine*. While the difference in time to discharge was just under 30 minutes, the authors say this is enough to improve patient flow in the emergency department.

> *"We believe there is clinical significance to 26 minutes, but there is a lack of evidence to guide what improvement in the time to make clinical decisions, or what improvement in total length of stay, should be considered clinically important."*
>
> — Aikta Verma, M.D.

Emergency department throughput is an important quality indicator. Waiting for laboratory results has been cited as a contributor to patients' length of stays in the emergency department.

In the present study participating physicians were randomized to receive troponin push alerts or not receive them (control). All patients who were treated by a participating physician during the study period (Feb. 1, 2014, to Oct. 15, 2014) and were discharged from the emergency department with a final diagnosis of chest pain were included. Chest pain discharges were chosen because the troponin would likely be the most important determinant of time to discharge. Participating physicians were not blinded to group assignment, as those assigned to the standard-of-care (no push alerts) needed to look up results on the computer.

The researchers found that over the study period, 1,554 patients were discharged from the emergency department with chest pain and of these 551 patients were part of the control group and 554 were in the intervention group.

The overall median interval from final troponin result to discharge decision was 79.7 minutes—94.3 minutes in the control group and 68.5 minutes in the intervention group. This 25.8-minute difference in medians was statistically significant. However, the total emergency department length of stay did not differ significantly between the groups.

"We believe there is clinical significance to 26 minutes, but there is a lack of evidence to guide what improvement in the time to make clinical decisions, or what improvement in total length of stay, should be considered clinically important," write the authors led by Aikta Verma, M.D., from the University of Toronto in Canada. "This will likely vary among institutions according to factors such as current length of stay and target length of stay ... The value of this intervention will depend on the costs and effects of other interventions available to each institution to improve length of stay."

Takeaway: Smartphone push alerts to notify physicians of laboratory results in significantly quicker discharges from the emergency department.

C-reactive Protein May Inform Antidepressant Medication Selection, *from page 1*

The researchers found that at baseline 37 of 51 participants in the SSRI monotherapy treatment arm had CRP level 1 mg/L or greater, as did 37 of 55 participants in the bupropion-SSRI combination treatment arm. Participants with low CRP levels (less than1 mg/L) performed "markedly better" with SSRI monotherapy than participants with higher CRP levels. In contrast, higher baseline CRP levels (≥1 mg/L) were associated with better outcomes with bupropion-SSRI combination. The researchers say these effects were evident as early as the second week of treatment. The overall remission rate was just over 41 percent. However, using CRP threshold-based assignment (SSRI monotherapy for less than1 mg/L and Bupropion-SSRI for at least1 mg/L) the estimated remission rate with was increased to just over 53 percent, with the number needed to treat of 8.6 to yield one additional remission. No baseline inflammatory marker was associated with side effect burden.

"The lack of moderator effect of serum amyloid P component and alpha-2-macroglobulin is novel and suggests specific role of systemic inflammation in predicting antidepressant treatment response," write the authors led by Manish Jha, from University of Texas Southwestern Medical Center in Dallas. "The implementation of treatment selection based on CRP level can be facilitated in busy clinical practices with the availability of point-of-care testing of CRP."

Takeaway: Baseline CRP levels may improve treatment for outpatients being treated for depression.