Put It on the Board, 2/14

When are genomic tests useful? IOM seeks answers

Collaboration among key stakeholders to set clear evidentiary standards is needed to determine the clinical utility of genome-based testing in cancer care, according to a wide variety of experts participating in an Institute of Medicine workshop.

Between 1969 and 1989, genomic biomarkers were mentioned in fewer than 50,000 National Library of Medicine publications. But between 2000 and 2010, more than 250,000 articles mentioned biomarkers, said a December 2013 IOM report, "Genome-Based Diagnostics: Demonstrating Clinical Utility in Oncology: Workshop Summary." The publication, which recaps a May 2012 meeting, is the work of the IOM's Roundtable on Translating Genomic-Based Research for Health. The group met again in early February to examine how the evidence for genomics is collected and assessed with respect to guideline development, coverage decisions, and clinical care.

The 21st century explosion of biomarker identification has frequently been accompanied by tests marketed "based on descriptive evidence and pathophysiologic reasoning, often lacking well-designed clinical trials or observational studies to establish validity and utility but advocated by industry and patient interest groups," Sean R. Tunis, MD, said at the 2012 meeting. Dr. Tunis is former chief medical officer at the Centers for Medicare and Medicaid Services and now president and CEO of the Center for Medical Technology Policy in Baltimore.

Dr. Leonard

Debra G.B. Leonard, MD, PhD, tells CAP TODAY there is a simple reason why the evidence for the clinical usefulness of genome-based testing is too often lacking. "We're just starting this work, plus there is a paucity of funding for such studies," Dr. Leonard says. "Basically, there aren't standards like there are for clinical trials about how you do good genomic studies, and what each study should be required to do, report, and analyze. So there are many bad studies out there. If you don't know how to look at these studies from a statistical, epidemiological perspective—or even consider the technical aspects of how testing was done—you could take those reports at face value and not be able to assess the quality of data, and determine that it's high-quality data or that it's data that's fatally flawed and should be thrown out."

Dr. Leonard is the CAP's representative on the IOM roundtable, which has secured participation from more than two dozen stakeholders including government agencies, drugmakers, medical geneticists, molecular pathologists, and health plans.

Setting the evidentiary standard for genomics is no easy task, says Dr. Leonard, professor and chair of pathology at the University of Vermont College of Medicine. She also is physician leader of pathology and laboratory medicine at Fletcher Allen Health Care in Burlington, Vt.

"It's very difficult to know how to look at the evidence when every individual who would participate in a clinical trial is genomically unique," Dr. Leonard says. "It's an n-of-one for each patient. Everyone is struggling with this new twist on evidence."

Experts acknowledge that setting the burden of proof too high could discourage genomic testing breakthroughs that would improve cancer care. Robert McCormack, PhD, co-chaired the IOM workshop and is head of technology

innovation at Janssen Diagnostics. His team developed testing for tumor cells in the blood in 2004, and began a study in 2006 to determine the test's clinical utility. Enrollment in the study was closed in 2012, and the team expects to determine the outcomes this year.

"It shouldn't take six years to [demonstrate the utility of a test]," Dr. McCormack said at the IOM's 2012 workshop. "We need to be creative to deliver the information that people want."

The key to improving patient outcomes is the ability to use genomic tests to select more effective therapies and reduce reliance on the empiric approach to treatment planning, says Massimo Cristofanilli, MD, who is not a member of the IOM roundtable. He is deputy director of translational research at the Kimmel Cancer Center and director of the Breast Care Center at Thomas Jefferson University Hospital.

"Just requesting a genomic test without having the tools to provide a better treatment to the patient is not effective," Dr. Cristofanilli tells CAP TODAY. "The therapy is the centerpiece of the effort we're trying to put in place for our patients. The improvement in survival will only happen when we match the ideal drug with the individual's tumor. This is the strategic approach to implementing personalized medicine. I know it's an abused term, and many institutions have developed different approaches, but we need consensus focusing on the translational aspects of genomics. This is the way it should be done."

For Renu Bajaj, PhD, uncertainty about payment is the biggest obstacle to moving forward with genome-based testing. She is Dr. Cristofanilli's colleague at Thomas Jefferson, directing the university's cytogenetics program.

"Hopefully, as we gather more data with regard to the various genetic testing and techniques used, reimbursement issues will be resolved," she says.

Payment is likely to depend on proof that genomic testing makes a difference in patient outcomes. In the IOM's report, Dr. Leonard is cited as calling for a clinical database that can be used to assess clinical utility and in guideline development and coverage decisions for genomic tests. Such collaboration is beginning to happen, with the National Institutes of Health establishing two databases—ClinGen and ClinVar—to provide freely accessible, public archives on discoveries and medical use of genomic variants.

"Pathologists, clinicians, other health care providers, and patients all need to understand what the evidence is, and not have every individual center interpreting this testing based only on their own test results," Dr. Leonard says.

"Genomics is very complex," she adds. "That's why a national effort is the right way to go and the best way to have the value created from genomics make an impact for our patients."

From Illumina: NextSeq and HighSeq X Ten

Illumina in January launched its NextSeq 500 System, which provides the power of high-throughput sequencing with the simplicity of a desktop sequencer. It has a one-day turnaround for a number of sequencing applications, including one whole human genome and up to 16 exomes, up to 20 noninvasive prenatal testing samples, up to 20 transcriptomes, up to 48 gene expression samples, and up to 96 targeted panels. The system is priced at $250,000.

For large-scale human whole genome sequencing, Illumina has introduced its HiSeq X Ten Sequencing System, which provides the throughput to sequence tens of thousands of human whole genomes in a single year in a single lab. Initial customers for the HiSeq X Ten are Macrogen, a global next-generation sequencing service organization based in Seoul, South Korea, and in Rockville, Md., where it has a CLIA-certified lab; the Broad Institute in Cambridge, Mass.; and the Garvan Institute of Medical Research in Sydney, Australia.

"For the first time, it looks like it will be possible to deliver the $1,000 genome, which is tremendously exciting," Eric Lander, PhD, founding director of the Broad Institute and a professor of biology at MIT, said in a statement. "The HiSeq X Ten should give us the ability to analyze complete genomic information from huge sample

populations. Over the next few years," he said, "we have an opportunity to learn as much about the genetics of human disease as we have learned in the history of medicine."

In other news, Illumina entered into an agreement with Amgen to develop and commercialize a multigene, NGS-based test as a companion diagnostic for Vectibix, approved in the U.S. for the treatment of metastatic colorectal cancer. The test will be developed for use with Illumina's MiSeqDx. The collaboration will seek to validate a test platform that can identify the RAS mutation status of patients for whom Vectibix would be appropriate.

Identifying aggressive prostate cancer

MDxHealth SA announced positive results from a study designed to identify patients with aggressive prostate cancer, presented at the Jan. 30–Feb. 1 ASCO Genitourinary Cancers Symposium in San Francisco.
In this study, the prognostic value of the epigenetic status of five genes (GSTP1, APC, RASSF1, RARB, and LGALS3) in 84 prostatectomy samples with different Gleason scores was evaluated. The results of a hierarchical clustering analysis showed that low gene methylation levels were detected in the vast majority of patient samples with GS6 and GS7 (3+4) prostate cancer. In contrast, respectively 81 percent and 91 percent of the GS7 (4+3) and GS ≥ 8 samples fell into the category with intermediate to high methylation levels.

VIDAS Galectin-3 validated

In a clinical research study published online in Clinica Chimica Acta, elevated galectin-3 levels in previously collected blood samples, measured using the bioMérieux VIDAS Galectin-3 assay, were reported to be significantly predictive of fatal cardiovascular events and severity of heart failure among the 137 patients diagnosed with chronic heart failure who were tested (dx.doi.org/10.1016/j.cca.2013.12. 017).
The prognostic information provided by the VIDAS assay in this study was found to be complementary and additive to that obtained by measuring BNP, NT-proBNP, and proBNP. The predictive value of galectin-3 levels was demonstrated to be independent of other key clinical parameters, such as impaired kidney function. When evaluated for analytical performance, measurement values obtained with the VIDAS Galectin-3 assay were found to be in agreement with those obtained with the BG Medicine Galectin-3 test.