Put It on the Board, 3/15

AMP outlines laboratory view on incidental findings

FDA sheds light on digital pathology standards

New guidelines for determining disease-causing potential of genetic variants

[hr]

AMP outlines laboratory view on incidental findings

The American College of Medical Genetics and Genomics' controversial 2013 recommendations on the reporting of incidental findings on select genes was the first attempt to address the matter in the clinical setting. But the ACMG's recommendations pose significant challenges that labs undertaking next-generation sequencing must be prepared to address, said a special report written by an Association for Molecular Pathology working group.

Dr. Hegde

Designed to provide a laboratory perspective, the AMP's report argues that the comparison of incidental findings in whole exome or whole genome sequencing to incidentalomas in radiology is "unfortunate." In genomic testing, "additional findings, beyond the genes analyzed to answer the clinical question that prompted testing, are not evident without significant extra effort directed toward that end," the article says (Hegde M, et al. *J Mol Diagn.* 2015;17[2]:107–117).

"The [ACMG] list is very important. If cancer is diagnosed early, there's a good possibility of implementing an appropriate treatment strategy," says Madhuri Hegde, PhD, chair of the AMP working group and executive director of the Emory University School of Medicine's genetics lab. "But for example, with PMS2, there are 16 pseudogenes that can interfere with analysis so certain regions of this gene cannot currently be done by NGS. That puts pressure and burden on the labs to use alternate methods such as Sanger sequencing."

The genome contains many such genes that can't be analyzed by NGS, and at least eight of the 56 genes on the ACMG list of recommended genes cannot be analyzed on the first pass and will require testing by alternative methods, she says.

"The complexity of NGS needs to be recognized," Dr. Hegde tells CAP TODAY. "The technological limitations of NGS don't allow us to look at all the genes with the same sensitivity and specificity."
Clearly explaining to ordering physicians the advantages and limitations of genomewide testing is one of the AMP's key recommendations.

"The report should be written so that it can be understood without the need for a high level of genetic knowledge and should avoid the use of scientific jargon," the article says. Setting out the testing's limits "is important because the ordering physician and the patient might believe that the lack of reporting of an incidental finding equates with a lack of pathogenic variants," the AMP says.

The AMP working group also advises that labs clearly state which genes will be analyzed in incidental findings,

report only pathogenic or likely pathogenic variants, and submit the list of pathogenic variants identified to public databases such as ClinVar and the Human Gene Mutation Database.

Ensuring the informed consent process is adequate is another area where the lab plays a key role, the report says. In addition to outlining in accessible language the pluses and minuses of testing, the laboratory's consent form should discuss the categories of variants reported (for example, diagnostic, carrier, or pharmacogenetic markers). The AMP report also backs the ACMG's 2014 clarification on opting out of learning about incidental findings. Dr. Hegde and her working group colleagues advise that the opt-out conversation take place during the discussion with a highly trained genetic counselor.

Of the referrals coming to Emory for whole exome sequencing, very few are opting out of receiving this information, but giving patients a choice is extremely important, Dr. Hegde says. "Most people want to know everything." That is not surprising, she says, given patients' low level of familiarity with the issue.

"The general public is not reading the literature," she says. "There are plenty of papers in the literature on the consequences of giving incidental findings. But the general public is reading articles in newspapers and magazines that say the technology is here to detect genomewide changes. The need for education in genomics both at the physician and patient level is heavily emphasized in this article."

[hr]

FDA sheds light on digital pathology standards

Draft guidance issued by the Food and Drug Administration in February lays out the agency's expectations for the technical specifications of whole-slide imaging devices used in digital pathology.

Dr. Pantanowitz

While the FDA document does not cover the more controversial area of what clinical data companies would need to submit to gain marketing approval for whole-slide imaging devices in primary diagnosis, Liron Pantanowitz, MD, says the agency's move is significant. He is a member of the CAP's Digital Pathology Committee and associate professor of pathology and biomedical informatics at the University of Pittsburgh Medical Center.

"For a while, there's been a lot of hype around digital pathology, and everyone's been very excited and ramped up and ready to go," he tells CAP TODAY. "There are lots of vendors in the market, and pathologists are buying these systems and wanting to get them going. But without any approval for primary diagnosis, it started losing momentum. We noticed our colleagues in Canada and Europe were able to do this, and we asked, 'Why not us?'"

"When we went back to the vendors and asked why they weren't getting premarket approval, they said it is very difficult and they need guidance from the FDA about what's required for premarket approval and clearance here," Dr. Pantanowitz says. "This is one step toward some guidance."

The 24-page document provides "serious detail," in Dr. Pantanowitz's assessment, about what the FDA expects manufacturers of these devices to demonstrate with regard to how their systems perform the task of acquiring whole-slide images and how those images are displayed and manipulated at desktop workstations. It also details how companies will be expected to test their devices. The draft guidance, open for comments through May 26, is available at https://federalregister.gov/a/2015-03843.

If the guidance is finalized, it could offer a peek inside the companies' proprietary systems and help pathologists and others better understand how the devices work and what their potential failure points may be, Dr. Pantanowitz says.

The agency has classified whole-slide imaging systems as class III medical devices, the highest-risk category of devices that are subjected to the premarket approval process. How, precisely, the FDA will evaluate digital pathology systems remains unclear.

"Hopefully, this technical guidance will be followed up with guidance on how to assess the clinical parameters for premarket approval," Dr. Pantanowitz says. "Do you need 2,000 cases? 10,000? How many centers do you need? Is it OK to use general pathologists, or do they have to be subspecialists? . . . I'm sure vendors would like to get this information up front so they don't have to argue back and forth and waste everyone's time."

Another critical question for the FDA to answer regards clinical endpoints. Must pathologists' diagnoses using glass be 100 percent concordant with their findings using digital images? Or is there some rate below that—perhaps the 95 percent concordance rate frequently seen in the medical literature—that would be acceptable?

Despite the lack of a clear road map from the FDA, some companies have begun the process of seeking premarket approval. Dr. Pantanowitz speculates that FDA approval of a whole-slide imaging system for primary diagnosis is at least two years away.

"I'm happy that the FDA seems to be listening to both the pathologists and the vendors in coming up with a document like this," he concludes. "We've previously never heard from them. We were asking lots of questions, but we never really knew whether they were listening. This shows they are." *—Kevin B. O'Reilly*

[hr]

New guidelines for determining disease-causing potential of genetic variants

In an effort to standardize interpretation and reporting of genomic test results, the American College of Medical Genetics and Genomics, together with the Association for Molecular Pathology and the CAP, has developed an evidence-based gene variant classification system and accompanying standard terminology (Richards S, et al. *Genet Med.* Epub ahead of print March 5, 2015. doi:10.1038/gim.2015.30).

The guidelines provide five standard classifications: "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign," with standard definitions for each term. These new standards may place more variants in the variants of uncertain significance category because there is insufficient scientific evidence to state with confidence that they do or do not cause disease, Sue Richards, PhD, chair of the workgroup that issued the guidelines, said in a statement. She is a medical director of Knight Diagnostic Laboratories and professor of molecular and medical genetics at Oregon Health and Science University.