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By Monica Heger

In an attempt to establish standards and consistency in the growing field of clinical next-generation sequencing, a workgroup for the American College of Medical Genetics and Genomics last week published guidelines in *Genetics in Medicine* for laboratories offering such tests.

"The point of the guidelines is to make this aspect of clinical molecular diagnostic testing somewhat more feasible for laboratories that aren't already doing it," Joshua Deignan, a member of the workgroup and assistant professor of pathology and laboratory medicine at the University of California, Los Angeles, told *Clinical Sequencing News*.

The ACMG workgroup's guidelines are similar to ones published by a US Centers for Disease Control-led group last year in *Nature Biotechnology* (*CSN 11/28/2012*).

The difference, according to Deignan, is that while the CDC group focused on test validation and proficiency testing, the ACMG group addressed other issues with clinical sequencing such as test ordering, reporting results, and dealing with low-quality samples. For example, the ACMG group included sample reports describing how to convey genomic information back to physicians.

The guidelines address issues related to next-gen sequencing panel tests, exome sequencing, and whole-genome sequencing, and essentially put into writing what many of the early laboratories adopting clinical sequencing have already discussed and put into place.

"They're very well done," David Bick, director of the advanced genomics laboratory at the Medical College of Wisconsin and medical director at Children's Hospital Wisconsin, told *CSN*. "All the guidelines, we've long since implemented," he added. These are mostly "pointed to laboratories that are just wanting to get into the next-gen game."

In addressing next-gen sequencing panels, the group recommends including only genes for which there is clear evidence of disease association. In broad panels covering overlapping phenotypes, "laboratories should consider providing a physician the option of restricting the analysis to a subpanel of genes associated to the subphenotype," the authors wrote, for instance, hypertrophic cardiomyopathy genes within a broad cardiomyopathy gene panel, "to minimize the number of variants of unknown significance detected."

The group gives similar recommendations for exome and whole-genome sequencing tests, suggesting that laboratories consider a phenotypic-driven analysis to limit the number of variants of unknown significance.

Additionally, the group emphasizes the need for understanding and communicating the limitations of next-gen sequencing tests. Exome capture kits, for example, miss many regions, some of which are medically relevant, and it is important for laboratories to understand exactly what regions are poorly covered or missed completely and to either fill in those regions with Sanger sequencing or communicate that variants in those regions cannot be called confidently.

Deignan said that this aspect of understanding and expressing the limitations of the test was something that his group at UCLA has since adjusted because of the development of the guidelines.

UCLA offers a clinical exome test, which Deignan said is not very good at calling large structural variants. As the ACMG group's discussions progressed, Deignan said the UCLA lab has now implemented a recommendation for ordering physicians that if they suspect that the patient's phenotype is caused by a large insertion or deletion, they consider other testing.

Deignan said that UCLA has established 10-base insertions and deletions as the cut-off, and will report indels up to that size but not greater.

Another issue the ACMG workgroup addressed was confirmation testing, writing in its guidelines that confirmation is "essential when the analytic [false positive] rate is high or not yet well established."

The group does not specify what type of confirmation testing should be used as long as it is orthogonal, but does say that Sanger is most frequently used. Nevertheless, it does leave room for laboratory directors to decide that in certain cases confirmation may not be necessary.

"In testing environments where confirmation of all results may not be possible before initial reporting (e.g., certain lower-risk incidental findings from ES/GS studies such as pharmacogenetic alleles for drugs not under consideration for the patient), it is recommended that laboratories clearly state the need for follow-up confirmatory testing," the authors wrote.

Bick said this is the one point he takes issue with in the recommendations.

"Inside our own lab, we had vigorous discussions about this," he said. The potential problem, he said, is that even if the report clearly states that confirmatory testing is still needed, "in the real clinical world, someone will overlook that warning."

"We've had instances when the next-gen result was incorrect when examined by Sanger," he said.

Deignan said that confirmatory testing was a major discussion among the group members, and said that the group wanted the guidelines to both acknowledge the current need as well as current limitations and give lab directors the freedom to "implement new ways of doing [confirmatory testing] in the future based on their experience," he said.

Whether these guidelines from the ACMG and CDC impact how next-gen sequencing tests are regulated in the future is still unclear. Deignan said that despite moves toward more standardization, it would still be difficult for the US Food and Drug Administration to broadly regulate next-gen sequencing tests. For instance, with exome sequencing tests, different laboratories use different capture techniques, different sequencing instruments, and different algorithms for variant calling and analysis.

"The reagents that labs are using are so broad and such a wide variety that I don't think the labs performing the same tests can agree on one set end-to-end way of doing the test," he said.

What might be more feasible for the FDA to regulate is a specific test or even instrument, Deignan said. For instance, Illumina has submitted its MiSeqDx system and two cystic fibrosis assays to the FDA for 510(k) clearance. An FDA-cleared cystic fibrosis assay using next-gen sequencing makes more sense than an FDA-cleared exome test, said Deignan, because such a panel "has a known indication and a set list of recommended variants."

Going forward, Deignan said that the ACMG may also tackle the issue of somatic mutations. The current recommendations focus primarily on tests analyzing germline mutations and Deignan said that separate guidelines would need to be developed for somatic mutations.

He said the group decided to keep the two separate since there would likely be issues specific to each type of test. For instance, confirmatory testing with Sanger sequencing is often not feasible with somatic mutations since they can be present at frequencies below Sanger's limit of detection.

The current guidelines also do not address incidental findings in much detail. Earlier this year, a separate ACMG workgroup issued guidelines related to incidental findings, recommending that pathogenic variants from a set list of 57 known disease genes be returned to the ordering physician regardless of patient preference.

Since their release, laboratories have been debating the pros and cons of such an approach, with many deciding to go against the ACMG's recommendations and offer patients the option to not receive those findings (*CSN 5/8/2013*).

"Depending on what happens, and whether those specific incidental findings guidelines are revised at some point, that section of our NGS guidelines could be revised," he said.

"There are definitely a lot of things that will be updated as the field gets more comfortable in this area," he added. "Right now, next-gen sequencing is a new technique to the clinical lab arena, but it definitely has potential and at UCLA is likely to become the new gold standard."

Monica Heger tracks trends in next-generation sequencing for research and clinical applications for GenomeWeb's *In Sequence* and *Clinical Sequencing News*. E-mail Monica Heger or follow her GenomeWeb Twitter accounts at @InSequence and @ClinSeqNews.

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