ACMG's Incidental Finding Guidelines At Odds with Policies of Some Clinical Sequencing Providers

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By Monica Hager

The American College of Medical Genetics and Genomics last week issued recommendations for reporting incidental findings from clinical exome and genome sequencing tests, citing 56 genes in which certain variants should be returned to the patient, regardless of the patient's actual preference.

While most in the clinical sequencing community lauded the ACMG for taking a stance on the issue, not everyone agreed that taking away patient choice was the right decision. And a number of early providers of clinical sequencing tests have already put in place their own policies that diverge a bit from ACMG's recommendations.

The guidelines were designed by an ACMG workgroup that was appointed in November 2011 and charged with the task of evaluating the utility of making recommendations for analyzing and reporting incidental findings from clinical sequencing. The ACMG board of directors approved the workgroup's guidelines at the organization's annual meeting in Phoenix, Ariz., last week.

The ACMG "did a great job in trying to highlight this very important problem," David Bick, the director of the advanced genomics laboratory at the Medical College of Wisconsin and medical director at Children's Hospital Wisconsin, told Clinical Sequencing News. MCW and Children's Hospital Wisconsin have been offering clinical sequencing since January 2010.

While Bick commended the ACMG for addressing the issue, he disagreed with the recommendation that specific incidental findings must be returned. "We feel that the patients and the parents are in the best position to make a decision for their family" in terms of what, if any, incidental findings are returned, said Bick. "It is the physician's and the genetic counselor's responsibility to explain the choice that these people are making."

The goal of the guidelines, explained Robert Green, a medical geneticist at Brigham and Women's Hospital and Harvard Medical School and co-chair of the ACMG working group, was to "design recommendations that will be relevant, not only for where [clinical sequencing] is now, but where it's going."

"The capability of the lab to customize a report doesn't scale well … when you start to imagine many genomes working through the medical establishment," he said.

Instead, having one standardized protocol for both children and adults that includes a list of genes that should be returned no matter what creates a much more scalable framework than customizing each exome or whole-genome sequencing test, he explained.

Green said the group discussed at length the issue of patient preference and decided that next-gen sequencing technology was "creating new opportunities and challenges that we thought necessitated divergence from the practices that are currently established for single gene testing."

"In this situation, as thousands and millions of genomes are rolled out in the coming years, we think the benefits may outweigh the risks," he added.

In terms of the actual gene list itself, the workgroup included genes involved in hereditary cancers, Marfan syndrome, long QT syndrome, Brugada syndrome, and certain cardiomyopathies, among others. In general, the syndromes had to have well-validated genes and variants for which confirmatory testing is available. The group also prioritized disorders for
which preventative measures and/or treatments are available and disorders in which individuals with pathogenic variants might be asymptomatic for long periods of time.

The group did not include genes related to disorders that would be included in newborn screening, nor did it address preconception sequencing, prenatal sequencing, newborn sequencing, or the sequencing of healthy individuals. The guidelines also do not apply to sequencing of research participants but only to sequencing performed in the context of a clinical diagnosis.

While a number of academic and commercial laboratories currently offer clinical exome or whole-genome sequencing, until now there has been no guiding framework for how to deal with incidental findings.

For instance, MCW returns results that the parents are interested in knowing, including incidental findings related to adult-onset disorders. Alternatively, parents can choose not to receive that information.

Baylor College of Medicine, meantime, offers both a focused and an expanded report. The focused report includes variants not necessarily related to the patient's disease, such as pharmacogenetic findings and other variants that the institution deems medically relevant. The report is returned to the physician, who then discusses with the patient what results he or she wants.

The expanded report requires an additional level of consent and includes disease genes that are not actionable, such as genes associated with untreatable neurologic conditions.

At the other end of the spectrum, the University of California, Los Angeles, only returns variants related to the patient's disease.

Whether laboratories currently offering such tests will change their practices based on these guidelines remains to be seen. MCW's Bick said that while he thinks it is "too early to be excluding families from the decision making," he said MCW would discuss the ACMG guidelines.

"For me, the hardest thing is going to be [figuring out] what's best for my patients, and I don't think that's been decided yet," he said.

Madhuri Hegde, scientific director of Emory's Genetics Laboratory, which began offering clinical exome sequencing in August 2012, told CSN that she would consider revising how the test is run based on the guidelines, but noted that Emory's own policies will be an important factor.

Similar to MCW, Emory has been returning incidental results based on physician preference. "We work closely with the physicians," she said. "We'll call them, discuss results both before and after releasing the report," she said.

Going forward, she said, the personal genome group within the laboratory will discuss the guidelines among themselves and also with the institutional review board and Emory's legal department. "I have to work according to the institution's policies. We'll get guidance from our IRB and our legal department," she said. "If advice is given to me by my institution, I'll follow that."

Hegde added that she thought the guidelines were a good start. "The community needs some guidance," she said. "This was a very courageous effort."

Laboratories that are just getting into clinical sequencing may find the guidelines useful. For instance, David Craig, co-director of the Translational Genomics

Research Institute's Center for Rare Childhood Disorders, said that TGen is "looking for others to lead" on best practices for returning results and that if there are guidelines, "we will likely modify our protocols to follow those guidelines," although at the time of the interview with CSN the guidelines had just been published and the center had not yet reviewed them.

Craig said that the center does around 70 percent of its sequencing in house and outsources the remaining 30 percent.

While the TGen center is eager for guidelines, Keri Ramsey, the center's clinical research coordinator, acknowledged that returning incidental findings to parents would be challenging.
"Some of our parents are even hesitant to receive information that they were the carrier of the gene responsible for their child's disorder," she said.

Green acknowledged that the guidelines would potentially pose a burden for new laboratories. "It will be an extra burden, extra cost, particularly for some cancer laboratories that aren't oriented around germline sequencing," he said.

Regulatory Impact?

Green said he anticipates that specialists and experts will review the guidelines and offer their own recommendations about genes that should either be added or taken away. "We assume that this list is a starting point and should be dynamic," he said. The group also recommended to the ACMG board that infrastructure be put in place for updating the list as new evidence is accumulated.

Another issue is whether lab accreditation groups like the College of American Pathologists will adopt the guidelines as part of their own requirements for next-gen sequencing tests. Last
year, CAP for the first time published a checklist specific to next-generation sequencing that labs must now follow in order to gain CAP accreditation (CSN 8/1/2012).

Nazneen Aziz, director of molecular medicine at CAP, told CSN that the ACMG guidelines are a "good first step" and are "important and timely."

However, she too would like to see patients given a choice to not receive incidental findings, even if the findings are actionable. She said one way this could be done, while still being scalable for large numbers of genomes, is to create "buckets" of results, such as 'adult-onset actionable' or 'adult-onset non-actionable.' The patient could then choose specific buckets during the informed consenting process with their physician, which would preserve autonomy while still creating a standardized approach, she said.

She said that CAP will definitely discuss the ACMG guidelines and consider whether to incorporate any of them into the CAP NGS checklist. The earliest they could be incorporated into the checklist would be 2014, since the deadline for submission to the Centers for Medicare and Medicaid for the 2013 checklist has already passed, she said.

What to include on the CAP checklist will be an "ongoing discussion" with an updated checklist published annually, Aziz said. "Every year we'll revise and clarify our language, or include things that we haven't considered before."