ACMG Clarifies Without Changing Recommendations on Incidental Findings; Labs Begin to Adopt

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By Monica Heger

The American College of Medical Genetics and Genomics last week issued a clarification to recommendations it released in March about how providers of clinical exome and whole-genome sequencing tests should deal with incidental findings.

The clarification was issued following feedback the organization received, both positive and negative. The organization did not change any of the guidelines, but sought to clear up what it felt were some misunderstandings.

Additionally, some labs are now considering adopting the recommendations, but with an opt-out option for the patient. This week, GeneDx and Ambry Genetics told Clinical Sequencing News that the firms have revised their policies in response to ACMG's recommendations, making them among the first to do so.

GeneDx said that the recommendations would be applied to its clinical exome test, but would include an opt-out option. Similarly, for all its exome orders, Ambry will now report ACMG's minimum list as a default, but like GeneDx, will give patients the opportunity to decline.

Additionally, the University of California, Los Angeles told CSN that it is now considering revising its guidelines. Currently, its consent form says that it will not report any incidental findings.

The guidelines, which were released at ACMG's annual conference in March, specify pathogenic variants in 57 genes related to 24 disorders that providers of diagnostic exome or whole-genome sequencing tests should evaluate and return to the ordering physician, regardless of the original intent for ordering the test and regardless of patient preference.

At the time, several providers of clinical exome and whole-genome sequencing

tests expressed concern that the guidelines were at odds with their current practices (*CSN 3/27/2013*).

Robert Green, a medical geneticist at Brigham and Women's Hospital and Harvard Medical School and co-chair of the ACMG working group that was charged with developing the guidelines, said the clarification "stands firmly behind the recommendations as initially offered and does a good job of further articulating the rationale" of those recommendations.

ACMG Executive Director Mike Watson agreed and told CSN that there is "no change at all" to the recommendations.

Bruce Korf, president of the ACMG Foundation for Genetic and Genomic Medicine and also a member of the workgroup that developed the guidelines, told CSN that ACMG decided to publish a clarification after commentary and feedback indicated that there were some misunderstandings about the guidelines.

For instance, he said, "there was a lot of pushback on the notion of not giving patients that opportunity to opt out of incidental findings," but much of the criticism was directed at returning variants of unknown significance, which the ACMG did not endorse, he said.

"That's not what we were proposing at all. The list of genes and variants that were identified were deliberately selected to only be confined to genes that had overwhelming clinical significance, overwhelming data to support that, and actionability," he said.

In ACMG's clarification statement, which is published on its website, the authors wrote that the "rationale for our recommendations was that not reporting a laboratory test result that conveys a near certainty of an adverse yet potentially preventable medical outcome would be unethical."

Green added that there has also been some confusion with regards to how the findings should be returned. ACMG is not suggesting that the test providers return such results directly to the patient, but to the ordering physician, he said.

"Discovering one of these variants is not an end in itself," he said. "It's a clue or a piece of evidence to be integrated with other evidence that the clinician may ask for, such as family history, the age of the individual, symptoms that might not have fit a pattern before."

The physician is the one who knows the family best and "is in the best position to consent them to the sequencing in advance, knowing that these incidental

findings could be returned," he added.

Additionally, ACMG reaffirmed that while it does not believe that children should be tested for adult-onset genetic conditions, it "believes that reporting an incidental finding of a severe, actionable, pathogenic mutation falls outside this recommendation," according to the clarification.

Korf elaborated and said that the group feared that if, for example, a breast cancer risk mutation was found in a child, then that mutation would have significant clinical importance for the child's parents. If the family did not know there was a history of early-onset cancer, then the finding of this mutation might be the only indication, and could potentially be life saving.

Additionally, knowing about the mutation in the child would enable physicians to monitor that child as an adult. And there is "no certainty that that would have come to light," when the child was an adult, said Korf.

Green said that ACMG is putting together a process for accepting suggestions for modifying the list variants that should be reported, but it does not plan to change the core principles of the guidelines.

Opt-out option

Despite the clarification, there are still those that are critical of the recommendations. Megan Allyse, a bioethicist at Stanford University, told CSN that the clarification still does not address the concern she has over patient autonomy. While the guidelines clarified what variants would be returned and how, they still recommend not giving the patient a choice to opt-out.

"The guidelines even go so far as to say that if a patient doesn't want the results of this new panel of tests, they should be denied whole-genome or whole-exome sequencing for their ongoing medical condition, which I think strikes many people as wrong," she said.

Additionally, she said that the guidelines essentially redefine the term incidental findings. Because the ACMG guidelines recommend specifically searching 57 genes for pathogenic variants, the results are no longer incidental, she said.

The "guidelines redefine incidental findings from something accidental to the target of a deliberate search: this is a significant change with a lot of implications for cost of care and access to medical services like genetic counseling," she said.

Sherri Bale, managing director of GeneDx, told *CSN* that the firm decided to adopt the recommendations in part, but provide an opt-out option.

"We're going against the recommendations and providing an opt-out," she said. "We didn't think it was appropriate to force people to get information that they may or may not have wanted."

Ambry has also made reporting ACMG's minimum gene list its default for all samples received after May 7, but is giving patients the opportunity to decline those findings, Elizabeth Chao, Ambry's chief medical officer, told *CSN*.

Ambry offers both a first-tier exome test, which comprises the 4,000 genes in the Human Mutation Gene Database, as well as a clinical diagnostic exome test, which is the full exome (*CSN 3/20/2013*).

The minimum gene list will be provided with both options, and the firm will also continue to give patients the option of receiving expanded secondary findings in its clinical diagnostic exome test, which include recessive disease genes, cancer predisposition, adult-onset disease predisposition, and early-onset disease. These options have been provided to patients since the test first launched in 2011, and patients can elect each individual category or none.

Wayne Grody, the former president of the ACMG, member of the working group that developed the recommendations, and director of the diagnostic molecular pathology laboratory within the UCLA Medical Center that provides a clinical exome test, told CSN UCLA is considering revising its guidelines.

UCLA, which launched its clinical exome test last year, has had a policy of only returning results related to the patient's condition and does not report any incidental findings (*CSN 3/7/2012*).

However, Grody said that "in practice, when they come up — and we have stumbled into BRCA mutations — we've usually called the ordering physician and discussed it candidly and how to or if to report it."

As a result of these incidents as well as in response to the ACMG recommendations, he said the laboratory is now in the process of re-evaluating its consent form. It is considering both adopting the guidelines as set by the ACMG and also including an opt-out option like GeneDx.

"It's the most difficult issue I've ever deal with in genetics," added Grody.