ACMG Mulls Minimum Gene List for Returning Secondary Findings from Clinical WGS

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By Monica Heger

A workgroup of the American College of Medical Genetics is devising guidelines to address issues related to returning secondary findings from clinical whole-exome and whole-genome sequencing studies.

Among the considerations is identifying a minimum list of genes for which information on variants should be returned — even when these genes are not implicated in the disease for which the sequencing was conducted.

The workgroup held a forum at last month's ACMG annual meeting where it outlined its current thinking on the issue and heard from stakeholders and other interested parties. Robert Green, the group's co-chair and associate director of Partners Center for Personalized Genetic Medicine at Brigham and Women's Hospital and Harvard Medical School, told *Clinical Sequencing News* that the goal is to issue the guidelines by June.

Green was also a co-author of a recent survey on genetics experts' opinions on what secondary findings should be returned to patients' physicians (*CSN 3/21/2012*). That paper was not related to the ACMG workgroup, he said, but was instead "an attempt to take a poll of different experts and see what they said that was in common and what they said that was not in common."

Green said that the ACMG group is focused on developing guidelines for the return of secondary findings in cases where whole-genome or whole-exome sequencing is being used in a clinical setting specifically to diagnose a condition, and that the guidelines will not address the use of sequencing in a research setting or the use of sequencing as a screening tool.

Among the ideas being considered is the creation of a minimum list of gene variants that would be standard to return to the ordering physician, regardless of whether they play a role in the primary disease under study.

"We wanted to float that idea," he said, "because we do think that as sequencing becomes more accurate and the analysis of genomes becomes more facile, that it will be technically fairly straightforward to identify certain types of mutations in certain disease genes," he said. "And some are going to be highly penetrant, well-recognized, pathogenic variants that are strongly suggestive of a possible present or future disease."

Genes being considered for the list include those for inherited cancer syndromes, Marfan syndrome, familial hypercholesterolemia, and Fabry's disease.

In all these cases, there are known or strongly suspected pathogenic variants with a "strong association between having the variant and eventually having the disease." In addition, "there is a well-accepted pathway for intervention" in these diseases, Green said.

On the other hand, a gene like APOE would likely not be on the list, because while variants to that gene have been associated with Alzheimer's disease, they have low penetrance and there is not yet an intervention.

Additionally, genes for mitochondrial disorders are also not currently being considered because variants in those genes can cause very variable disease presentations.

There are also a number of genes that fall into a gray area, said Green. For some of those genes, there is simply not enough data about the prevalence of the variants in the general population.

"There's no data to guide us [as to] whether certain variants in the general population, in the absence of symptoms or family history, will go on to create phenotypes," Green said.

For example, while variants have been associated with hypertrophic cardiomyopathy, this has mostly been in the context of individuals who already have symptoms or who have a strong family history.

However, the disease has the potential for a severe initial presentation, so knowing a patient had predisposing variants could help in monitoring and screening for the condition.

Additionally, variants associated with biotinidase deficiency have an unclear meaning in asymptomatic individuals, but there is a simple treatment for the disease.

Green said that if the group does in fact end up creating a minimum gene list, it will not be static. As sequencing technology and understanding of disease improves, genes would likely be added or removed from the list.

A "mechanism for continual reassessment and revision" would have to be built into the guidelines, which will likely be uncomfortable for medical practitioners who are used to guidelines that remain in place for at least a few years, Green said.

The group is now addressing many of the issues that were raised during the ACMG forum on the topic as well as reaching out to additional experts, before issuing its guidelines in June.

Green emphasized that the guidelines would not be obligatory, but rather suggestions on how to navigate an emerging and often confusing field.

"The alternative is to leave every lab and clinician on their own, to figure out their own path," he said.

He said the group is not in discussion with the US Food and Drug Administration about whether the ACMG's recommendations could influence how the FDA eventually regulates next-gen sequencing-based diagnostics.

The group will also not address how genetic counseling should be delivered. The focus is not on dictating how clinicians should practice medicine, but rather to give clinical labs some guidance on how to return secondary findings from sequencing to ordering physicians, Green said.

"How somebody uses that information — the decisions they make, the consultants they bring in — that's not something we would try to comment on," he said.

The ACMG guidelines will only address sequencing in a clinical setting, and not sequencing that is done under a research protocol that allows for return of results.

This distinction is important, said Green, because sequencing-based research protocols are all so different, and can vary from sequencing from biobank samples where there is no interaction between the researcher and subject, or the sequencing could be done by a researcher who is also a clinician and does has family history and extensive phenotypical data on the patient.

Clinical Contextualization

Going forward, bringing sequencing into the clinic will requirement the same kind of clinical infrastructure present in other medical fields.

This clinical infrastructure is critical for contextualizing sequencing results, Green noted. For example, X-ray results are never returned to the patient directly from a radiologist, said Green. If someone relatively young and healthy had a bicycle accident and suspected a broken rib, but then an X-ray uncovered an abnormality that could potentially be a lung tumor, the radiologist would not return that result directly to the patient, he noted.

Instead, it would be returned to the clinician who would then be able to take that finding and put it into context, rather than reporting to the patient that he or she might have a tumor. The clinician would ask about the patient's smoking history, health, age, and be able to either recommend further follow-up testing, or deem additional tests unnecessary.

Additionally, Green said that ACMG's guidelines will not address sequencing performed as a screening tool — by a healthy person curious about his or her genome. Currently, he said, it's unclear whether sequencing will become a widely used screening tool in the medical environment, and at least in the near future, "most medical sequencing will be ordered for a cause, a diagnostic workup of some kind, not necessarily for screening," he said.