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You Didn't Ask For These Genomic Test Results, But They Might Save Your Life

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Say you have a mysterious heart ailment and, through your doctor, you are getting clinical genome sequencing to discover the molecular cause of that condition. Do you think that the laboratory that performs your sequencing should also seek out and report other unrelated genetic abnormalities, such as a genetic variation that increases your risk for familial cancer?

Most people do, but not all. And questions about how to manage such "secondary" or "incidental" findings have generated a great deal of debate.

In 2013, I led a working group of the American College of Medical Genetics and Genomics (ACMG) that created the first guidelines on secondary findings. Our recommendation: When labs provide clinical sequencing for any medical condition, they should also include medically important findings in a minimum list of 56 genes that are associated with 24 different genetic conditions. This particular list of genes became known as the "ACMG56." Updated secondary findings guidelines were published in November 2016, which modified the recommended minimum list to 59 genes, and changed the preferred nomenclature to "ACMG SF v2.0".

The ACMG recommendation is that abnormal findings or "pathogenic variants" for these genes be returned along with the results of *any* medical sequencing — even if the lab is looking for something completely unrelated, and even if you have no family history of the disease associated with the secondary finding. The problem is, pathogenic variants don't

necessarily pose the same degree of risk for everyone. If you have a pathogenic variant but no family history of the condition it's linked to, it's not clear that you truly have a higher risk of that condition.

What's been missing in this debate is hard evidence that pathogenic variants in a small group of genes actually increase the risk of developing the related condition. But such an experiment is hard to do because families affected by the ACMG secondary findings genes are quite rare.

We decided to study this by focusing on people who had received genome sequencing as part of epidemiological research and were *not* selected for a family history of the 24 conditions in the original ACMG recommendations. We collaborated with researchers at the Framingham Heart Study in Massachusetts and the Jackson Heart Study in Mississippi whose study participants had just been sequenced as part of the research. Then we asked two questions: How often would pathogenic variants in the ACMG gene list turn up? And when those variants were found, how often were they associated with clinical signs of one of the associated conditions?

At first blush, our hypothesis might seem obvious. Shouldn't anyone who has a pathogenic variant associated with a disease show increased risk of that disease? But, in fact, genetics has traditionally studied families that have both altered genes and disease. The correlation between pathogenic variants and clinical features had never been demonstrated in large groups of people who were not first selected for family history.

The study took over two years, but was finally published in the journal Science Translational Medicine a few months ago. We found that almost exactly 1% of the populations in both FHS and JHS carried a pathogenic variant in one of the original ACMG56 genes. And we found that those carrying pathogenic variants had an increased aggregated risk of developing clinical features associated with the corresponding diseases.

As always, though, it wasn't quite that simple. For one thing, while people with a pathogenic variant did show significantly increased chances of having clinical features related to one of the 24 diseases, they did not *all* have those clinical features. In other words, many people who had a pathogenic variant for at least one of those 24 diseases did not yet show any signs of *having* any of those diseases.

The debates about secondary findings end up reflecting the sensibilities about public health screening and prevention. Some experts will look at the 1% of the general public who are carrying pathogenic variants and say: "Returning these results to everyone could improve — or even save — the lives of one in every 100 people!" Others will look at the same data and say: "Returning these results to everyone does nothing for 99% of all people, and may even harm some of the remaining 1% who will never develop the disease in question."

Yet with this work, we have established that in the aggregate, pathogenic variants in the ACMG genes are associated with future disease. Discussion about the clinical utility of

the ACMG minimum list is far from settled. But with these results, we may be a few steps closer to consensus.

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