Genome Sequencing for Healthy People: Will it be Helpful?

by Robert C. Green, MD

More and more laboratories are offering genome sequencing for apparently healthy individuals. This "predispositional" sequencing covers a large panel of genes, or even a person's whole genome or exome—and unlike most medical sequencing, it is available to people with no specific medical condition or concern. At first, the notion of sequencing as "screening" sounds pretty great. It can cover hundreds, or even thousands of genes, a deep dive that you can't get from consumer genetic tests (yet), and it's ordered by your doctor, who can help you process any important results that turn up.

But while it is clear that for someone with mysterious symptoms or with a family history of disease, genome sequencing offers clear benefits, it's a bit more complicated for persons who want to be sequenced in order to reveal risks of future health problems.

Most of the debates about genome sequencing for apparently healthy people involve at least one of these concerns:

1. Will it be helpful? (How many apparently healthy patients will actually receive useful, actionable results?)
2. Will it be harmful? (How will patients handle results? Will the process cause unnecessary anxiety or lead to unnecessary medical tests and procedures?)
3. Will doctors be able to handle it? (Will physicians be able to understand and use this information in a way that helps, and does not harm, the individual?)

Our paper, published this summer in *Annals of Internal Medicine,* sheds some light on all of these questions. The paper reports results from the MedSeq Project, the first NIH-funded clinical trial studying whole genome sequencing in medical practice, guided by a multidisciplinary team of more than 40 scientists.

The Annals paper reports on a part of the MedSeq Project that followed 10 primary care physicians and 100 of their generally healthy middle-aged patients. Half of the patients received a family history report on their genetic disease risks, while the other half received both a family history report *and* a personalized whole genome sequencing report. This was the first randomized trial to study the impact of whole genome sequencing for apparently healthy patients.

Some of our most surprising results so far relate to that first all-important question: "Will it be helpful to anyone?"

Out of the 50 apparently healthy MedSeq Project participants to receive whole genome sequencing, we estimated that just one or two would have a genetic disease variant in their report. But to our surprise, 11 of those 50 participants

(22 percent) learned that they carried a genetic risk variant for a rare single-gene disease. While the result bears some caveats, particularly the small sample size, the fact remains that this was definitely a higher number than we had expected.

Now, of the 11 participants who had a rare disease variant, only two showed symptoms of the associated disease. The two diseases that did connect to existing symptoms were not terribly serious. One was an eye condition that impairs night vision, the other a skin condition that causes rashes and sun sensitivity. Not particularly drastic, or enlightening, except that these individuals had never known the etiology of these "minor" health complaints.

The other nine participants with disease variants showed no outward signs of those diseases. If they do appear later, however, some of those conditions, such as heart rhythm abnormalities could be life-threatening. These are the kinds of results that lead doctors to recommend action, or that encourage patients to take actions of their own. Here we find the most potential for benefit—but also the most potential for harm.

When asked six months after receiving their results, 41 percent of those 50 patients reported making a health behavior change, including the ones whose reports contained nothing of concern. For comparison, 30 percent of those who received a family history report but no genome sequencing made a health behavior change. This may be an area for further study; even if the sequencing report itself provides no specific guidance, does the process of receiving the report lead some people to make positive behavioral changes?

We also demonstrated that in the first 6 months after the intervention, those who were sequenced did not have a dramatically different medical course than those who were not in terms of follow-up testing. In an economic analysis included in the Annals paper, there was no significant difference recorded between the medical expenses of the two groups. This is important since a common and powerful argument against using genome sequencing for screening suggests that it will lead to a dramatic proliferation of medical expenses of questionable value.

So, back to the question: Will it be helpful? Will medical genome sequencing provide a substantial benefit to a significant number of apparently healthy patients? Like any good researcher, I would answer this with phrases like "more research is needed" and "it depends," both very true in this case. But these early results suggest that yes, whole genome sequencing may very well be substantially helpful to a significant number of healthy patients.

But will it be harmful to other patients? And how will doctors handle all of this information? Stay tuned—we'll get to those questions in the next post.

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