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Genome Sequencing for Healthy People: Is it Time?



By Robert C. Green, MD, MPH

It may be true that we have entered the age of personal genomics, but we have only just scratched the surface.

Hundreds of thousands of patients have now received genetic testing over the past 2 decades through health care providers — usually targeting specific genes or gene panels linked to rare hereditary conditions.

And over 2 million people have sent their DNA samples to private companies and received reports on genotype markers that provide information about ancestry, carrier status for specific diseases and other health-related traits. Genotyping looks only at specific parts of the genome, markers that have (with varying levels of certainty) a meaning attached to them. Most of the time, the markers identified by genotyping are common variations that have a small effect on risks for common conditions. In one case, you might find out that your genotype markers “raise” your risk of diabetes from 44% to 46%. A few genotypes can reveal more substantial risks. Common [APOE](#) variants, for example, can be revealed by genotyping, and they are associated with a substantial increase (3-10x your baseline) in risk for Alzheimer’s disease.

Genotyping might look at a few million of these letters, but leaves 99% of your genome unexplored. This is where the new sequencing technology comes in. Instead of targeting specific markers, whole genome sequencing allows us to decode all 3 billion letters of a person’s DNA. This opens up many exciting possible applications in health care. For one thing, the sequence can function like a reference library to be consulted as new knowledge comes to light. People who “own” their genome sequence, probably living on a server somewhere taking up [anywhere from 1 to 200 gigabytes](#), may be able to search their personal DNA code to see how each new medical discovery applies to them.

But whole genome sequencing has only recently becoming affordable and is now being used in medicine primarily for cancer treatments and to find the molecular etiology of mysterious illnesses that are suspected of being genetic. What we haven’t done is

integrate personal genome sequencing into our everyday lives and routine medical care.

The integration of sequencing into health care doesn't fit very well in the model of how medicine is practiced today, but is well aligned with the future vision of health care that so many of us have — a vision that focuses upon prediction and prevention.

We imagine that personal genome sequencing could play a central role in bringing about a more personalized and participatory form of medicine — including a health care system where patients have more knowledge of their own risks and diagnoses and are empowered to act upon that information.

With that in mind, more of us are asking this question: Rather than focusing only on people with a suspected or diagnosed genetic disease, why not also use genome sequencing to help seemingly healthy people screen for all sorts of conditions, even diseases for which they have no known family history?

We refer to this idea as “predispositional personal genome sequencing,” or PPGS. And if it sounds like something that should already be commonplace, it isn't. While many groups of sick individuals, and some cohorts of healthy people have been sequenced, only a small number of people (we estimate fewer than 2,000) have been sequenced and received their results afterward.

We are not yet at the point where a healthy patient walks into a doctor's office and arranges to have her genome sequenced to scout for potential future problems, but that's the direction we're headed. Debra Leonard, chair of pathology and laboratory medicine at the University of Vermont College of Medicine and UVM Medical Center, predicted to the Wall Street Journal that by 2023, “we will be sequencing every patient.”

There are still quite a few things holding back such broad use of personal genomics. The cost of genome sequencing may be the first barrier that comes to mind, but that cost is dropping all the time. Other expenses may end up being bigger factors, accounting for the time, knowhow, and computing power needed to translate each person's mountain of genomic data into a comprehensive and decipherable report. And it may be quite some time, if ever, before health insurance companies start covering genome sequencing as a preventative measure for healthy people.

There are also legitimate concerns about using sequencing as a screening tool. What if people misinterpret or overreact to their results and spend their money or take health risks trying to address a condition they might never actually develop? What if low risk results cause some people to become complacent about their health? And what if those types of insurance that are not currently protected by law start discriminating against individuals who learn of new and previously unanticipated genetic risk factors?

Perhaps the most important unanswered question is whether or not the presumed utility of PPGS will prove true. Will learning genetic risk information save lives, or could it possibly produce more harm than good? If this question leaves you scratching your head, consider this example: if genetic risk variants that increase the risk of cancer are disclosed to 100,000 people and their doctors order additional x-rays to try to detect

those cancers, could the exposure to x-rays end up causing more cancer?

We don't have all the answers yet. Through our NIH-funded [MedSeq](#) and [BabySeq](#) Projects, we are tracking the short and long-term results of genome sequencing in a medical setting, but so far no large-scale study has systematically tracked seemingly healthy individuals for the years that it would take to measure whether or not this improved their lifetime health.

So how do we start tracking the outcomes of those individuals who are already arranging to be sequenced out of curiosity or in the hopes of preventing future illnesses? We've started by organizing the Personal Genome Sequencing Outcomes Consortium, or [PeopleSeq](#). It's an ambitious project in which we are hoping to track many of the "genome pioneers" who have been sequenced with return of results. It's going to take years, but we already have some interesting preliminary findings to share! Stay tuned, and we will discuss these in my next posts.

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