Genetically sequencing DNA could yield patient care insights

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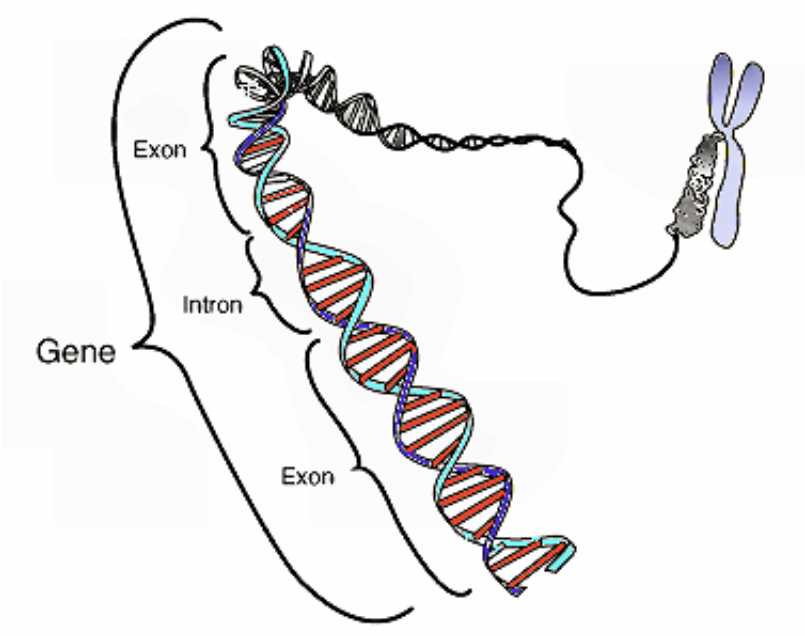

This image shows the coding region in a segment of eukaryotic DNA. Credit: National Human Genome Research Institute

Increasingly, the words "genetics" and "genome" are making their way into news stories about health and medicine. Doctors talk about scientific research—how there may be links between gene mutations in your DNA and an increased risk of cancer or heart disease—but it all seems far away, like something that's not quite connected to your own health and well-being right now. And up until recently, that was true. To accurately identify those links, researchers would need to know how

often a genetic mutation occurred among the U.S. population. To know that, they'd have to do large-scale genetic sequencing, which was prohibitively expensive.

But recently the institutional cost of sequencing a person's protein-coding genes, called whole-exome sequencing (WES), went down to less than $1,000 per person. Only then did the possibility of relying on genetics as a part of preventative medicine—looking for gene changes before they cause symptoms—emerge. We're closer to the point where this information can have a significant impact on your health care today.

Now Yale Medicine and Yale New Haven Health, along with several other institutions across the country, are beginning to offer WES as part of very large studies designed to discover more information about the role of genes, and gene variants, in disease. Yale's project has set a goal to enroll 100,000 participants over the next five years to create a biobank, or repository, of volunteers' blood samples. With sequencing results, these will link to the individual's electronic health record. By correlating medical histories with the presence of genetic mutations on a large scale, researchers and physicians hope to make more headway in the still-nascent field of genomics.

Leading the project is Michael Murray, MD, clinical director of Yale's new Center for Genomic Health. Dr. Murray comes to New Haven from Geisinger Health in Pennsylvania, where he helped build the country's first DNA biobank. There, researchers sequenced the exomes of more than 50,000 patient volunteers. Then, they took it a step further and followed up with each patient whose gene variants turned out to be linked to disease or cancer. Four of five volunteers had no idea about their risk before joining the study. These patient volunteers were then directed to doctors who could advise them on what steps they could take to protect their health.

It's important to note, however, that for now relatively few participants in studies like this will receive such a call. That's because the pool of genes linked to genetic diseases that could benefit from preventative care remains very small. But that's likely to change as more data are collected, says Dr. Murray.

Dr. Murray answered more questions about Yale's genetic sequencing project and the hope it holds for personalized medicine.

How is the biobank project at Yale different from genetic tests done in the clinical setting or at-home kits?

It's different in many ways. What we are doing is high-quality, whole-exome sequencing in partnership with the Yale Center for Genome Analysis. This facility is CLIA-certified, meaning it meets federal standards for quality control and testing. We also keep individual genetic data on file for future research as more gene variants are discovered. When that happens, we will circle back and let participants know about these new findings. This isn't possible with single genetic tests currently done in the clinical setting. Finally, we aren't selling a product. This isn't a genetic test. This study is for scientific discovery. If people are concerned that they have a genetic variant based on family history, they should schedule an appointment with their doctor.

How will large-scale genetic sequencing like this contribute to precision medicine care?

Within this project we'll identify patients who have a genetic change that puts them at risk for cancer or heart disease. We'll provide that information to them and help them get appropriate care for it. There will also be opportunities to invite patients back for additional studies. We

plan to start out searching for just under 60 known gene variants that, once discovered, could alter a patient's medical care. But that list will grow as we gain a better understanding between gene variants and diseases.

In the end, the biobank we build will be very useful to researchers. By using de-identified data, researchers can ask all kinds of questions. For example, a study could focus on people who are 25 years old and have diabetes and look at what genetics are involved across that group. Once you have a big enough group with enough data, you can ask many different types of questions.

How many academic health centers have genomic centers like this?

So the number is one. Just Geisinger.

What was the most difficult aspect of creating it?

How many hours do you have? It had never been done before. We had to create a way to identify and confirm the information and then deliver it to the electronic health record, so it could be received by the patients and providers. Then, the information had to be explained to both of them and the patient had to receive care based on best practices. So, an enormous infrastructure has been set up that doesn't exist in any healthcare system except Geisinger now. That's really the big work ahead.

In a recent study, you found that, at least in the patient population at Geisinger, the BRCA1 and BRCA2 variants [known as the "cancer genes"]

occurred in men and women more frequently than previously thought, right?

For the past decade, the expectation established in medical literature was that the likelihood of any U.S. man or woman carrying a variant in the BRCA1 or BRCA2 genes—which are linked to a higher risk of breast, ovarian, prostate, and pancreatic cancers—was 1 in 400. And for those of Ashkenazi Jewish ancestry, the estimate was 1 in 40.

But for this group of about 50,700 patients enrolled in the Geisinger study, who were older and of European background, the risk was closer to 1 in 190. That's twice as often. We think a couple things are going on. One is that we've underestimated how frequently people have these gene changes. The other is that the current approach to identifying who needs genetic screening is completely inadequate. In the same study, of the 267 people who carried the BRCA1 and BRCA2 variants, 82 percent did not know. So, there's a real value in performing this kind of sequencing on a large scale.

How can people volunteer to be a part of this biobank project?

We will have a website with detailed information. Our goal is to have opportunities throughout the Yale Medicine and Yale New Haven Health offices for people to sign up, so it will be easy to join. It will also be easy to withdraw from the project if participants change their mind or decide they do not want to be contacted about a genetic variant found in their sequencing results. But the hope is that people will want to be a part of this project because it is contributing to how medicine and health care are delivered.

Is there something that drives your enthusiasm for

this?

I'm trying to come up with a great answer for you. We will have patient success stories. That's why I get up and go to work in the morning. Somebody finds out something that they didn't know was important, and they can do something about it and avoid a life-threatening disease. So, preventative intervention through genetics is kind of the core. And hopefully next year around this time, we'll have people from here telling those stories. That's really what it's about. We're changing medicine, and that's pretty cool.

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