Patient's whole genome reveals risk of diseases and adverse drug responses

April 29 2010

Scientists at Stanford and Harvard Universities collaborated to assess the clinical usefulness of analyzing a patient's full genome for disease risks and unusual drug responses. The work brings closer to reality the concept that whole-genome sequencing might one day play a clinical role.

For the first time, researchers have used a healthy person's complete genome sequence to predict his risk for dozens of diseases and how he will respond to several common medications. The risk analysis, from the Stanford University School of Medicine, also incorporates more-traditional information such as a patient's age and gender and other clinical measurements. The resulting, easy-to-use, cumulative risk report will likely catapult the use of such data out of the lab and into the waiting room of average physicians within the next decade, say the scientists.

"The $1,000 genome is coming fast," said cardiologist Euan Ashley, MD, assistant professor of medicine, referring to the cost of sequencing all of an individual's DNA. "The challenge lies in knowing what to do with all that information. We've focused on establishing priorities that will be most helpful when a patient and a physician are sitting together looking at the computer screen."

Priorities that include whether a certain medication is likely to work for that particular patient, or if it's likely to have adverse side effects. Priorities that include ascertaining how a patient's obesity or smoking

combine with his or her inherent genetic risk for - or protection against - heart attack or diabetes. In short, priorities that result in concrete clinical recommendations for patients based on a degree of data that has never existed before.

"We're at the dawn of a new age in genomics," said Stephen Quake, who is the Lee Otterson Professor of Bioengineering. "Information like this will enable doctors to deliver personalized health care like never before. Patients at risk for certain diseases will be able to receive closer monitoring and more frequent testing, while those who are at lower risk will be spared unnecessary tests. This will have important economic benefits as well, because it improves the efficiency of medicine."

But it may also tell patients things they don't want to know.

Quake made national headlines last August when he used a technology he helped invent to sequence and publish his own genome for less than $50,000, and it is his genome that the researchers analyzed in this newest study. Ashley is the lead author of the research, which will be published in the May 1 issue of the *Lancet*.

An accompanying article about the ethical and practical challenges of such research, authored by a subset of the researchers involved in the first study, will appear in the online-only version of the *Lancet* on the same day. Hank Greely, JD, professor and director of Stanford's Center for Law and the Biosciences, is the senior author of the online piece.

"Patients, doctors and geneticists are about to hit by a tsunami of genome sequence data. The experience with Steve Quake's genome shows we need to start thinking - hard and soon - about how we can deal with that information," said Greely.

"When combined with other sources of information, genomics has the

power to predict the diseases a person is most likely to develop and how he or she might respond to certain medicines," said Jeremy Berg, PhD, director of the NIH's National Institute of General Medical Sciences, which funded a portion of the works. "This work provides a glimpse of how genomics can play a role in personalizing the medical care of individual patients."

The study began when the 40-year-old, seemingly healthy Quake asked Ashley's opinion about a particular snippet in his genome associated with an inherited disease called hypertrophic cardiomyopathy. People with the condition have enlarged hearts that don't beat effectively and are at risk for sudden cardiac death. Quake was interested because a distant relative had died unexpectedly in his sleep at the age of 19 - presumably from some type of heart problem. Ashley, who runs Stanford's Hypertrophic Cardiomyopathy Center, was alarmed.

"Given his family history and the particular genetic variation Steve has, I recommended that he be screened for the condition," said Ashley. Quake agreed, but the conversation got the two thinking about how to analyze the information in Quake's genome on a more global level.

"Several of us had already been thinking about how you would take someone's genomic profile, and translate what's in the billions of base pairs in that DNA to something that's clinically useful," said Ashley, who headed the group of geneticists, physicians, bioinformaticians and ethicists involved in the study. "Then we realized, 'Hey, we already have someone's genome.'"

What's more, Atul Butte, MD, PhD, assistant professor in bioinformatics, and his lab members had already done a lot of the necessary leg work: They'd spent the previous 18 months meticulously cataloguing publications that associated particular genetic changes called SNPs (for single nucleotide polymorphisms) with effects on specific

diseases. It was the first time anyone had compiled all the information in one database.

"We read thousands of publications," said Butte, "and we made a list of every single spot in the genome where we know that, for example, the letter A raises the risk of a particular disease, or the letter T confers protection. And then came Steve with his genome, and we were ready."

Together the researchers designed an algorithm to overlay the genetic data upon what was already known about Quake's inherent risk - based on his age and gender - for 55 conditions, ranging from obesity and diabetes to schizophrenia and gum disease. For example, as a 40-year-old white male, Quake entered the study with a 16 percent chance of developing prostate cancer in his lifetime. But as the computer, based on Quake's genomic sequence, began to incorporate the data of study after study, his risk scooched first lower, and then higher. (The researchers weighted the contribution of each variant according to the number, and sample size, of published studies confirming the association.)

In the end, after incorporating information about 18 separate variants from 54 studies, they determined Quake's risk of prostate cancer is actually about 23 percent. The opposite is true for his risk of Alzheimer's disease, which began at 9 percent and ended - due to the presence of several protective variants - at about 1.4 percent. The scariest monsters in the closet, however, were obesity, type-2 diabetes and coronary artery disease, each of which Quake has a more than 50 percent chance of developing, and each of which can affect the development of the other.

Was it alarming?

"It's certainly been interesting," said Quake of the findings. "I was curious to see what would show up. But it's important to recognize that

not everyone will want to know the intimate details of their genome, and it's entirely possible that this group will be the majority. There are many ethical, educational and policy questions that need to be addressed going forward."

Of course, a person's environment - in the form of choices he or she makes about diet, exercise and habits like smoking and drinking - can also powerfully affect disease risk. But if clinicians know that a patient has a higher-than-normal risk for a certain disease, they may recommend certain lifestyle changes more strongly.

"This opens the door to targeted environmental interventions based on a patient's genomics," said Butte. "People who may want more control over their destiny could choose to exercise more, or eat better, or even avoid pesticides more conscientiously."

There's hope, too, in the promise of more effectively using available drugs to combat or prevent disease. Russ Altman, MD, PhD, is the principal investigator of the Stanford-managed Pharmacogenetics and Pharmacogenomics Knowledge Base, or PharmGKB - a curated, international data repository to help researchers understand how genetic variation among individuals contributes to differences in reactions to common medications. Quake's genome gave his group some new opportunities.

"With Steve, we thought, 'Let's apply everything we know about the effect of human genetic variation on drug response to his entire genome,'" said Altman, who together with Quake chairs Stanford's bioengineering department. "And we came up with a table of drugs that are likely to work well for him, like statins, and others that he might need lower doses of, like warfarin."

The researchers also found five to 10 previously unknown SNPs in genes

involved in drug response. "This is really exciting because we never would have found these if we'd just relied on our usual panel of SNPs," said Altman. "What's more, with whole-genome sequencing, you only ever have to do it once. Our understanding of the information will keep evolving, but the core data set doesn't change."

That evolving knowledge base will present a particular challenge, the researchers believe. Keeping people up-to-date on new findings involving genetic variants that they carry will be a tricky business. Clinicians of the future will walk a tightrope of informing people who've opted to have their genome sequenced of ongoing discoveries while also presenting the information as uncertain and likely to change. Furthermore, how shall we deal with the fact that a patient's genome by definition harbors information about that person's parents, children and other relatives who may not want to peek into their shared genomic crystal ball? Clearly we have much with which to grapple.

"The world of medicine is going to change beyond belief," said Ashley. "We are all going to have to learn how to deal with questions like these."

But what of Quake?

A complete physical pronounced him free of any sign of cardiomyopathy. But it also turned up somewhat elevated lipoprotein levels. Normally, given Quake's health and age, most physicians would take a watch-and-wait approach before recommending medication. However, in the face of this new information about Quake's lifetime genetic risk, and the likelihood, based on the pharmacogenetic data, that he would respond positively to statins, Ashley suggested he consider taking the cholesterol-lowering drugs. It's the first time anyone's ever made clinical recommendations based on a cumulative assessment of a patient's entire genome.

And so it begins.

More information: Ashley EA, Butte AJ, Wheeler MT, Chen R, Klein TE, Dewey FE, Dudley JT, Ormond KE, Pavlovic A, Morgan AA, Pushkarev D, Neff NR, Hudgins L, Gong L, Hodges LM, Berlin DS, Thorn CF, Sangkuhl K, Hebert JM, Woon M, Sagreiya H, Whaley R, Knowles JW, Chou MF, Thakuria JV, Rosenbaum AM, Zaranek AW, Church GM, Greely HT, Quake SR, Altman RB. Clinical assessment incorporating a personal genome. Lancet, Volume 375:Pages 1525-1535, May 1, 2010.

Provided by National Institutes of Health

Citation: Patient's whole genome reveals risk of diseases and adverse drug responses (2010, April 29) retrieved 30 April 2024 from https://medicalxpress.com/news/2010-04-patient-genome-reveals-diseases-adverse.html

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