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First-ever integrative 'Omics' profile lets scientist discover, track his diabetes onset

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Geneticist Michael Snyder, PhD, has almost no privacy. For more than two years, he and his lab members at the Stanford University School of Medicine pored over his body's most intimate secrets: the sequence of his DNA, the RNA and proteins produced by his cells, the metabolites and signaling molecules wafting through his blood. They spied on his immune system as it battled viral infections.

Finally, to his shock, they discovered that he was predisposed to type-2 diabetes and then watched his blood sugar shoot upward as he developed the condition during the study. It's the first eyewitness account — viewed on a molecular level — of the birth of a disease that affects millions of Americans. It's also an important milestone in the realization of the promise of truly personalized medicine, or tailoring health care to each individual's unique circumstances.

The researchers call the unprecedented analysis, which relies on collecting and analyzing billions of individual bits of data, an integrative Personal "Omics" Profile, or iPOP. The word "omics" indicates the study of a body of information, such as the genome (which is all DNA in a cell), or the proteome (which is all the proteins). Snyder's iPOP also included his metabolome (metabolites), his transcriptome (RNA transcripts) and autoantibody profiles, among other things.

The researchers say that Snyder's diabetes is but one of myriad problems the iPOP can identify and predict, and that such dynamic monitoring will soon become commonplace. "This is the first time that anyone has

used such detailed information to proactively manage their own health," said Snyder. "It's a level of understanding of health at the molecular level that has never before been achieved."

The research will be published in the March 16 issue of *Cell*. Snyder, who chairs the Department of Genetics, is the senior author. Postdoctoral scholars Rui Chen, PhD, George Mias, PhD, Jennifer Li-Pook-Than, PhD, and research associate Lihua Jiang, PhD, are co-first authors of the study, which involved a large team of investigators.

The study provides a glimpse into the future of medicine — peppered with untold data-management hurdles and fraught with a degree of self-examination and awareness few of us have ever imagined. And, despite the challenges, the potential payoff is great.

"I was not aware of any type-2 diabetes in my family and had no significant risk factors," said Snyder, "but we learned through genomic sequencing that I have a genetic predisposition to the condition. Therefore, we measured my blood glucose levels and were able to watch them shoot up after a nasty viral infection during the course of the study."

As a result, he was able to immediately modify his diet and exercise to gradually bring his levels back into the normal range and prevent the ongoing tissue damage that would have occurred had the disease gone undiagnosed.

Snyder provided about 20 blood samples (about once every two months while healthy, and more frequently during periods of illness) for analysis over the course of the study. Each was analyzed with a variety of assays for tens of thousands of biological variables, generating a staggering amount of information.

The exercise was in stark contrast to the cursory workup most of us receive when we go to the doctor for our regular physical exam. "Currently, we routinely measure fewer than 20 variables in a standard laboratory blood test," said Snyder, who is also the Stanford W. Ascherman, MD, FACS, Professor in Genetics. "We could, and should, be measuring many, many thousands."

For Snyder, one set of measurements was particularly telling. On day 301, about 12 days after a viral infection, his glucose regulation appeared to be abnormal. Shortly thereafter his glucose levels became elevated, prompting him to visit his primary care physician. On day 369, he was diagnosed with type-2 diabetes.

"We are all responsible for our own health," said Snyder. "Normally, I go for a physical exam about once every two or three years. So, under normal circumstances, my diabetes wouldn't have been diagnosed for one or two years. But with this real-time information, I was able to make diet and exercise changes that brought my blood sugar down and allowed me to avoid diabetes medication."

Snyder started his study in the months after arriving at Stanford in 2009, when whole-genome sequencing of individuals was just becoming a reality. Stephen Quake, PhD, who is Stanford's Lee Otterson Professor of Bioengineering, had recently completed the complete sequencing of his own genome and was working to use the information to predict his risk for dozens of diseases.

But while the predictive power in genomic information is due in part to its static nature — because it doesn't change over time, a one-time analysis can hint at future events — our bodies are dynamic. They use our DNA blueprints to churn out RNA and protein molecules in varying amounts and types precisely calibrated to respond to the changing conditions in which we live. The result is an exquisitely crafted machine

that turns on a dime to metabolize food, flex our muscles, breathe air, fight off infections and make all the other little adjustments that keep us healthy. A misstep can lead to disease or illness.

To generate Snyder's iPOP, he first had his complete genome sequenced at a level of accuracy that has not been achieved previously. Then, with each sample, the researchers took dozens of molecular snapshots, using a variety of different techniques, of thousands of variables and then compared them over time. The composite result was a dynamic picture of how his body responded to illness and disease.

A number of molecular cues led to the discovery of Snyder's diabetes. His genomic sequence suggested he had an increased risk for high cholesterol, coronary artery disease (which he knew already), as well as basal cell carcinoma and type-2 diabetes, which was unexpected. Conversely, the sequence predicts his risk for hypertension, obesity and prostate cancer is lower than that of other men his age (54 when the study started). A check of his triglyceride levels at the start of the study confirmed that they were high: 321 mg/dL. Snyder took the cholesterol-lowering drug simvastatin, and his levels dropped dramatically to 81-116 mg/dL. Based on the type-2 diabetes prediction, the team decided to also monitor Snyder's blood sugar levels, which were normal when the study began.

Snyder, who has two small children, experienced two viral infections during the course of the study: one with rhinovirus (at day 0), and one with respiratory syncytial virus (beginning at day 289). Each time, his immune system reacted by increasing the blood levels of pro-inflammatory cytokines — secreted proteins that cells use to communicate and coordinate their responses to external events such as an infection. Snyder also exhibited increased levels of auto-antibodies, or antibodies that reacted with his own proteins, after viral infection. Although auto-antibody production can be a normal, temporary reaction

to illness, the researchers were interested to note that one in particular targeted an insulin receptor binding protein.

The researchers also sequenced the RNA transcripts present in Snyder's cells during infection at an unheard-of level of detail. "We generated 2.67 billion individual reads of the transcriptome, which gave us a degree of analysis that has never been achieved before," said Snyder. "This enabled us to see some very different processing and editing behaviors that no one had suspected. We also have two copies of each of our genes and we discovered they often behave differently during infection." Overall, the researchers tracked nearly 20,000 distinct transcripts coding for 12,000 genes and measured the relative levels of more than 6,000 proteins and 1,000 metabolites in Snyder's blood.

In Snyder's case, the researchers observed unexpected relationships and pathways between viral infection and type-2 diabetes by comparing the results of a variety of "omics" studies. "This study opens the door to better understanding this concerted regulation, how our bodies interact with the environment and how we can best target treatment for many other complex diseases at a truly personal level," said Li-Pook-Than.

The researchers identified about 2,000 genes that were expressed at higher levels during infection, including some involved in immune processes and the engulfment of infected cells, and about 2,200 genes that were expressed at lower levels, including some involved in insulin signaling and response.

"We were looking for common pathways that were changing in response to infection," said Snyder. "In a study like this, you are your own best control. You compare your altered, or infected, states with the values you see when you are healthy."

Snyder's iPOP is a proof of principle that the researchers hope will lead

to a more-streamlined, less-complex version for regular use in the clinic.

"In the future, we may not need to follow 40,000 variables," said Snyder. "It's possible that only a subset of them will be truly predictive of future health. But studies like these are important to know which are important and which don't add much to our understanding.

"Right now, this type of analysis is very expensive. But we have to expect that, like whole-genome sequencing, it will get much cheaper. And we also have to consider the savings to society from preventing disease."

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