GETTING PERSONAL

GENOMIC DNA TESTING THROUGH THE UVM HEALTH NETWORK USHERS IN THE FUTURE OF DIAGNOSIS

BY ELEANOR OSBORNE | PHOTOGRAPHY BY ANDY DUBACK

It was the longest 30 minutes of his life. Sitting in his office in the ground floor of the UVM Medical Center's main campus, Michael Towle stared at his computer while, in the office just down the hall, Debra Leonard, M.D., Ph.D., chair of pathology and laboratory medicine at the Larner College of Medicine, studied his genetic blueprint. Leonard was looking to see if Towle had the mutation for frontotemporal dementia (FTD), a devastating disease that strikes early.

A half-hour later, Leonard called him in to her office to tell him the good news: he did not have the mutation. Then, together, they cried.

A few years earlier, spurred on by the record of dementia and cancer in his family, Towle had decided to have his genome sequenced. After his mother began showing symptoms of FTD, the family asked William Pendlebury, M.D., professor emeritus of pathology and laboratory medicine at the Larner College of Medicine, to recommend and order genetic testing for their mother to try to identify the mutation causing FTD in their family. That information, along with the sequencing of Towle's genome, gave Leonard the scientific crystal ball she needed to predict Towle's chances of getting the disease. >>

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THE VOCABULARY OF GENOMICS

Genes: The inherited information in our body's cells is written in DNA code and packaged in these units.

Genome: An individual's complete set of genes plus the sequence in between the genes. Almost all our body's cells contain two complete copies of the human genome, which contains about 20,000 to 25,000 genes located on 23 pairs of chromosomes. Understanding the role of variations in our DNA code is very important for understanding disease.

Genetics: The study of genes

Genomics: The study of genomes

Towle is the only one of his siblings who's had his genome sequenced to find out whether he had the mutation. "I wanted to be able to prepare," he says. "And I wanted to know if my kids were at risk." But even as he sat in his office waiting, his resolve wavered. "I was doubting myself, then I was sure it was the right thing to do, then I was doubting myself again—it was an endless loop of uncertainty. Finding out put an end to the cycle. It was powerful."

PLAYING THE HAND YOU'RE DEALT

In poker, as in life, many of us think in terms of doing the best with what we have. By that way of thinking, what if you could learn your lifetime risks for disease.... and act accordingly?

That's the idea behind the genetic testing currently being offered to patients at select UVM Medical Center primary care offices. The test, provided at no cost as part of each patient's preventive health care, identifies differences in an individual's DNA that make certain diseases such as cancer and heart disease more likely. Results are protected in the patient's medical record, along with all the rest of their medical information.

Leonard, founder of UVM Health Network's Genomic Medicine Program, sees the integration of genetic testing into clinical care as an important next advance to traditional health care. "Genetics influences your overall health and longevity. We want to bring this into medical practice in a safe and effective way." With this in mind, the initial goal of the project is to test 1,000 patients by the fall of 2020 and 50,000 patients over five years.

The test, which is being offered at no cost, is coordinated through the UVM Health Network Genomic Medicine Program and is powered through partnerships with two companies—Invitae, a West Coast company specializing in clinical genetic testing, and LunaDNA, a platform that provides a patient-centric research database. What makes the LunaDNA platform unique is that it lets patients who opt to share their genomic and health information for research control how that information is shared for research. "Genetic information is a commodity," says Robert Wildin, M.D., associate professor of pathology and laboratory medicine and pediatrics and associate medical director of genomic medicine. "This platform gives patients control over how their information is used."

Further, says Wildin, "It's really important that we get this right, because the relationship between DNA differences and disease is worked out through research. Without data from real people that helps us distinguish normal DNA differences from disease-promoting ones, we can't advance the knowledge on when and how to apply this information to the clinic."

A WINDOW ON THE FUTURE

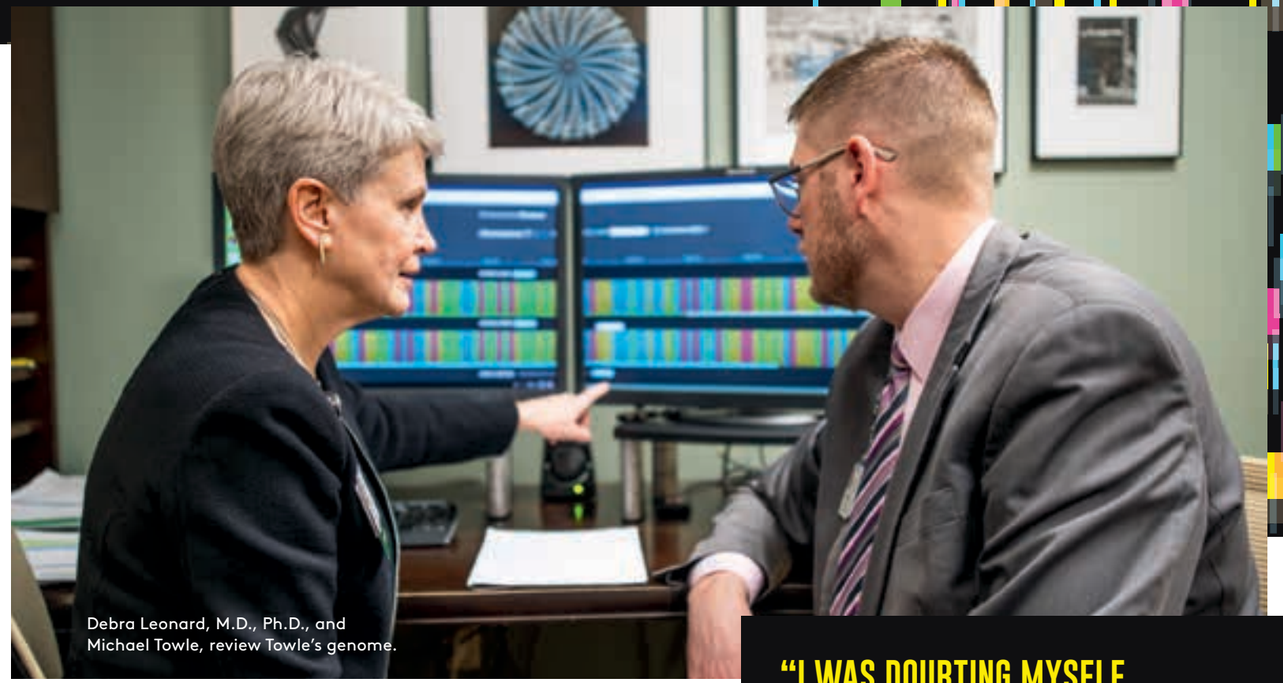
Using just two teaspoons of blood, the two-part test provides two things. First, a genetic health screen of 147 genes for cancer and cardiac risk. These are mostly genetically "dominant" disorders, so if a person has a positive result, they have an increased risk of having or developing the condition, and each of their children has a 50 percent chance of inheriting the same increased risk.

Secondly, the testing provides a carrier screen that targets 301 genes for genetically recessive conditions like cystic fibrosis. Most people are carriers of at least three recessive health conditions, most of them rare. Carriers have one altered copy of the gene, and one "normal" copy which prevents the disease. To have the disease a person needs to have received an altered gene copy from each of their parents. Thus, if you are a carrier, only if your partner also is a carrier would you have a chance of having a child affected by the condition. If both parents are identified as carriers, there's a 1 in 4 chance for each child to have the disease.

The UVM Medical Center laboratory sends the blood to the Invitae, a company based in San Francisco, which does the sequencing and interpretation of the results. Each patient receives a full report of their test results and an action plan created by genomic medicine experts at UVM Medical Center. If a patient has a positive result on the genetic health screen, family members can get tested for the positive results for free, as long as they do so within 90 days. Partners of carriers identified in the carrier screen can get tested at a reduced cost.

Setting expectations is an essential part of the process. Pre- and post-testing consultation with their primary care doctor or a genetic counselor helps patients understand the different results possible—and appropriate actions. If, for example, the evidence supports taking preventive measures, then patients should act, with support from their physicians. If a patient shows an increased risk that could affect them at a later age, or learn about something that isn't fully understood yet, then their doctor may counsel them to not do anything, at least for the present. Finally, if evidence indicates that the results are not likely to influence their health or their family's health—now and in the future—patients may be advised to move on.

The overall aim is to set expectations appropriately, and to provide patients with information that is linked to established treatment guidelines. "This pilot is using a very targeted approach," says Aaron Reiter, M.D., one of several primary care physicians currently offering the test. So far about 20 patients from his practice have enrolled, and, he says, people have generally been receptive to the idea. "For some patients, their families have never talked about why Uncle Bob died at the age of 50. Just getting some information about their genetic blueprint can be comforting. What I tell them is that this is one more data point we can reference—for now and in the future." For those patients who tell him that genetic testing makes them nervous, he asks, "Does it make you nervous to have your blood pressure checked or your cholesterol levels measured?"



Debra Leonard, M.D., Ph.D., and Michael Towle, review Towle's genome.

A VILLAGE SETS THE STAGE

Behind the scenes, a team of health care professionals and patient advocates has been involved in developing clinical care pathways aimed at making the process safe and easier for providers and patients. Key participants in the group leading the effort included primary care and specialist physicians and administrators from UVM Medical Center and a group of patient and family advisors. The team also includes Timothy Lahey, M.D., professor of medicine at the Larner College of Medicine and director of clinical ethics at UVM Medical Center.

The care pathways provide common language for every aspect of the experience, from obtaining informed consent to guiding patients on next steps, such as which specialist a patient should be referred to and what kind of further testing the patient might need before seeing the specialist. "We're learning a lot about genes as we get more information," says Christine Giummo, a genetic counselor involved with the program. "It's important for the family medicine doctors counseling these patients to have the information they need about further specialty care and testing so that they can advise accordingly. We have created the Genomic Medicine Resource Center to answer questions and provide resources for providers and patients."

Giummo notes that the care pathways' work is an evolving process: the team continues to adjust the pathways as patients and providers report on their experience, and as clinical evidence in the medical literature advances.

Striking the right ethical balance has also been a key focus. Ethical guidelines have helped shape the informed consent, to ensure that patients have a clear understanding of what the program offers, what the results can mean—and what kind of control they have over their information. Further, says Lahey, the ethical implications of knowing what your future holds have influenced the architecture of the pilot project. "We've been very careful. We don't want to give scattershot information that might lead to increased anxiety and unnecessary testing that ultimately isn't helpful. We want to offer information that is clearly connected to evidence-based pathways of care."

Community members who bring the patient and family voice to health care have played a role in ensuring that all the informational materials are understandable for patients and their families. Says Patient and

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Listen to a UVM Healthsource podcast with Dr. Leonard titled "What Personalized Medicine Means for You": med.uvm.edu/vtmedicine/web-extras

"THE PROMISE OF GENOMIC-INFORMED MEDICINE IS TO IDENTIFY DISEASE RISKS AND MISSED DIAGNOSES, GET TO THE RIGHT TREATMENTS FASTER AND AVOID INEFFECTIVE TESTS AND TREATMENTS."
— ROBERT WILDIN, M.D.

Family Advisor Brian Harwood, "We worked hard to make sure the words used matched the intent of the program, and were understandable for patients," he says. "There was a lot of merging ideas and compromising."

Leonard feels strongly that this collaborative approach will help ensure the program's success. "Our overarching goal is to do no harm. We always want to make sure our processes are safe and effective - and that patients have control over the use of their personal health information."

Lahey is encouraged by the careful, toe-in-the-water way the Genomic Medicine Program is wading into this work. "The focus is pragmatic, the goal is to be evidence-based, and the aim is to use genetic information thoughtfully."

THE GENOME AND VERMONT'S HEALTH CARE LANDSCAPE

If a patient who has no signs or symptoms learns they have a genetic difference that indicates the potential for lurking heart disease, the physician would order an echocardiogram. It's likely that this test wouldn't have been ordered in patients without recognized symptoms. How will these cause-and-effect ramifications of genetic testing impact our statewide efforts to reduce the overall cost of health care? How will we prove, in the long run, that genetic testing helps prevent future disease when incorporated into clinical care?

OneCare Vermont, Vermont's Accountable Care Organization (ACO), is well-positioned to view the results of genetic testing through the lens of cost effectiveness across the population. OneCare has already made a very significant contribution to the genetic testing currently being offered in primary care. Because an ACO can waive federal laws preventing health care organizations from offering innovative services for free, OneCare Vermont has given the program such a waiver so the genetic testing offered in this pilot is available to patients for free. This is a key factor in avoiding the bias associated with expensive procedures that can only be accessed by those who can afford them.

Norman Ward, M.D., associate professor of family medicine and chief medical officer, OneCare Vermont, says he's proud of the work that's been done thus far. "This is one of the first examples of an ACO and a statewide group of stakeholders wrestling with an issue of this scope and complexity. While there are certainly plenty of questions out there for the future, for now I think it is safe to say that the Vermont payment model and our ACO structure makes us uniquely positioned to assess the value of genetics in routine medical care."

POWER AND PROMISE OF THE UNKNOWN

The potential for genetic testing stretches far out on the horizon, marked with immense potential—and unanswered questions. Genome sequences and heath information about individuals could contribute significantly to scientific research, helping us understand how DNA differences are connected to our health

But hanging over all this is the as-yet unknowns. How do we manage this technology so that people who learn about their genetic blueprint get information that is truly useful to them? How can we prevent anxiety and needless further testing? How can we manage the cost implications?

In an ideal scenario, genetic testing would give patients and providers more information about their health and health risks. Timing of interventions could come before the onset of clinical disease. The number and types of tests could be tailored to the patient, using the test results as a guide. Patients and providers would have clear paths for making effective use of the information they learn from testing. Ultimately, genetic testing could lead to better care at equal or lower cost.

"This is an area of information impacting our health that we've never consistently integrated into health care," says Wildin. "Understanding how our genes impact health care is another tool in the tool box for providers and patients who can use it to make decisions about their care." VM

WITH THE FLICK OF A SWITCH

An avid runner, Greg Merhar sprinted his way through his early years before he became plagued by pain and intermittent fatigue.

"There was never an injury they could pinpoint," he says. "It was incredibly frustrating and limiting."

Still, he persevered, cutting out the backs of his sneakers so he could keep running through swollen Achilles tendons and taking medications to ease the pain. In college, a mysterious new symptom appeared: he felt like he had a bowling ball rolling around his stomach. This, too, came and went, with no apparent cause.

MRIs and upper GI studies revealed nothing. His doctors told him he needed a vacation.

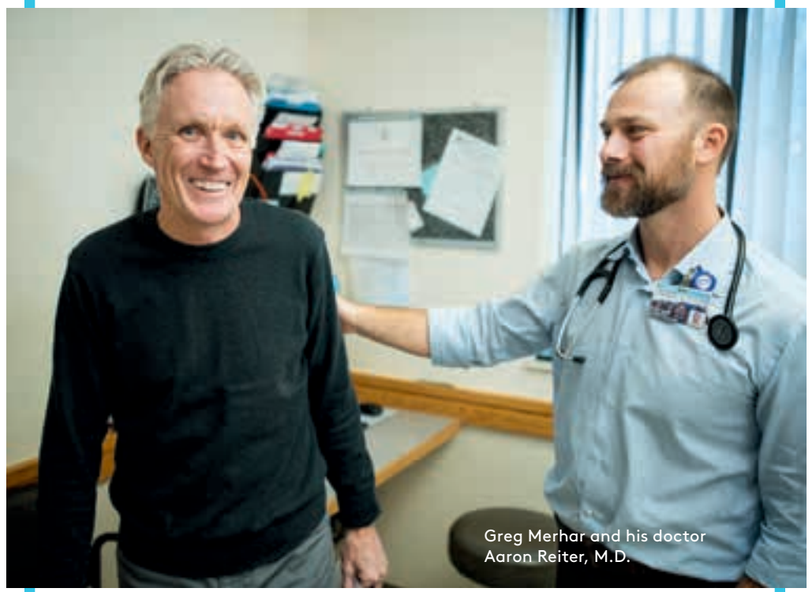
Flash forward four decades. Merhar and his wife Debra Leonard, M.D., Ph.D., the founder of UVM Health Network's Genomic Medicine Program, decided it would be romantic if they gave each other their genome sequences for Christmas.

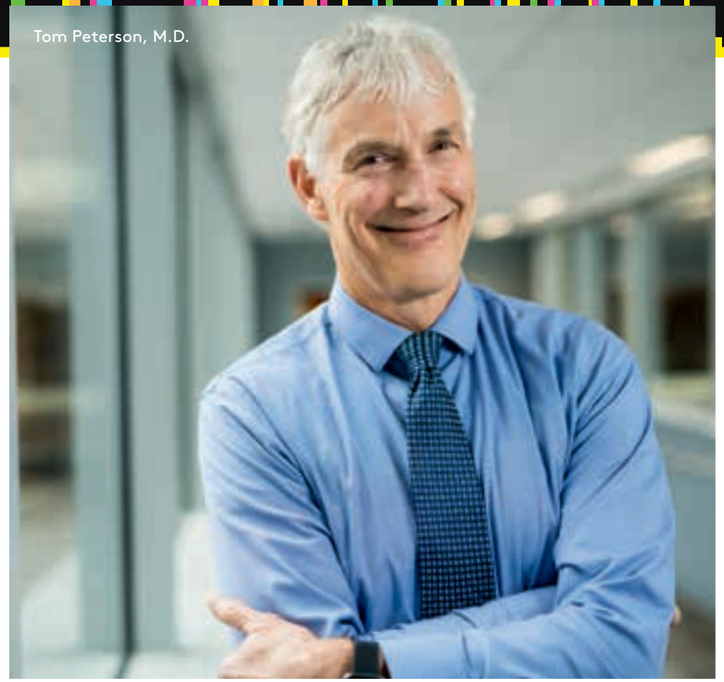
As it turned out, for Merhar, this was a life-altering gift. The sequencing revealed that he has a genetic mutation on chromosome 16. With a little sleuthing, he also learned he fit the profile for Familial Mediterranean Fever (FMF), a condition in which his body doesn't produce any or enough of a protein that is involved in helping to regulate the process of inflammation. "Basically, any inflammatory event, I just blow up," he says.

Within a few days, he had a prescription for Colchicine. He took it Friday night. Saturday morning he woke up feeling like "a light switch had gone off." Sunday morning, he lay in bed and thought, "I have no pain."

Merhar points out that because he doesn't look like someone of Mediterranean heritage, it wasn't a diagnosis that would have occurred to the many physicians who saw him over the years. "In that way I'm kind of the poster child for genetic testing," he says. "That was the key to my diagnosis."

Today, Merhar is still running. And every step of the way, with every passing year, the image of a man beset by pain recedes into the rear view mirror.


Greg Merhar and his doctor Aaron Reiter, M.D.


Tom Peterson, M.D.

A PHYSICIAN'S EXPERIENCE

Tom Peterson, M.D., physician leader of UVM Medical Center's primary care service line, sees the world through the dual lens of scientific inquiry and curiosity. Guided by these overlapping perspectives, in April of 2014 he signed on to have a full mapping of his genome—all 20,000 or so genes.

As a physician and a scientist, he was drawn in—and then there was the personal: with a history of cardiovascular disease in his family, he wanted to know if additional risk for that was in store for him as well. "I had some trepidation," he says. "But it wasn't too daunting."

To look into what may be your future can be daunting, and information revealed through genetic testing can lead to more uncertainty. "Genetic testing is one of many examples of how our technology sometimes outpaces our understanding," he says. "We have to be mindful of how we use it."

His own results were encouraging—and useful. Not only was there nothing especially concerning, but the sequencing revealed important information about how his body metabolizes medication. Further, he says, "I have a unique level of confidence knowing that my entire genome is stored on a thumb drive."