Secrets packed away in a family's genome are increasingly being found—and discussed

by David Cameron

legacy

Joseph Thakuria was facing an impasse. ■ He stood at a whiteboard in a conference room where a group of patients, all members of an extended family, sat around a table. They had come to him out of desperation. For generations, seemingly healthy family members in the prime of life had, without warning, died of a thoracic aortic aneurysm. The indiscriminate nature of the affliction was shaking the psychological well-being of the family tree. No one knew where they stood. Doctors were out of ideas. As a last-ditch effort to find answers, this band of relatives had come to Thakuria, a medical geneticist at Massachusetts General Hospital.

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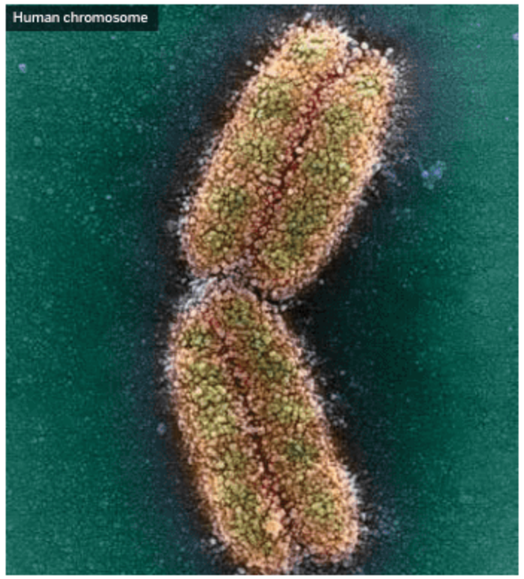
GOOD COUNSEL: Medical geneticists like Joseph Thakuria and Joan Stoler work with patients and their families as they learn of heritable conditions uncovered in analyses of the genetic information contained in their chromosomes.



Human chromosome

JENNIFER SARBAH (FAR LEFT); ADRIAN T. SUMNER/SCIENCE PHOTO LIBRARY

TRACY AIGUIER

Using the investigatory skills that specialists like Thakuria are known for, part science and part detective work, he and his colleagues solved the mystery. Careful and intensive genome sequencing had fingered the causative mutation.

While knowing the identity of the genetic culprit would not point to a cure, it would allow physicians to screen family members. Those in the clear could breathe easy, while those bearing the DNA signature could take preventive measures.

Thakuria ushered the family into a conference room to explain all this—and to give each of them the option to be tested for the mutation. More than a dozen members of this extended family listened, rapt, as Thakuria described the diagnosis buried in their genes. Then, he asked each of them the million-dollar question: Do you want to know?

"Not everything in genetics is 100 percent certain and predictive the way it was for this particular family," says Thakuria, who also is an instructor in pediatrics at Mass General. "But there really is no correct answer to this question."

One by one, members of the family agreed to be tested. Then one said "no." He preferred to continue receiving annual echocardiograms rather than knowing which genetic cards he'd been dealt.

His relatives thought he was nuts. Each of them took him to task, insisting that there was only one sane answer to the question. Dodging the genetic test was simply not rational. In the hope of breaking the tension, Thakuria jumped in.

"I tried to explain that this was like deciding what to do with lottery money," he says. "It's different for everybody. There's no right or wrong."

The individual stuck to his decision, and, in the end, everyone was right. But what should medicine do when the patient is a family and the diagnosis implicates generations?

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A Change of Pace

Over the past decade, the science of genetics has accelerated at a rate that makes Moore's Law look like a slacker. Thanks to advances in technology platforms like microfluidics, printing out a patient's genetic code could soon become as routine as taking blood for a cholesterol test.

As Thakuria and his colleagues continue to incorporate more in-depth genomic sequencing into the clinic, researchers will need to grapple not only with a whirlwind of information, but also with patients and doctors who will struggle over how to interpret the results.

In short, the world of genetics is undergoing a revolution. But like all major cultural and technological insurgencies, the attendant issues raise a host of medical, social, ethical, and even psychological concerns.

Take Thakuria's foray into family therapy. Decades ago, the majority of known genetic disorders were rare, and often chromosomal. Today researchers know of nearly 5,000 such disorders. Not more than a decade ago, medical geneticists relied on physical examinations and phenotypic clues, while genetic testing yielded only the crudest data, confined primarily to single gene analyses and to locating large structural rearrangements, such as the extra chromosome that causes Down syndrome or the string of nucleotide repeats associated with Huntington's disease.

But the clinical use of genetic testing has now caused an information surge that the medical establishment is struggling to manage. Today, a person can spit into a tube, send the sample to any number of direct-to-consumer companies and, for as little as one hundred dollars, receive a scan of genetic markers—known variations in DNA that can be used to identify a person, species, or disease—that indicates susceptibility to conditions such as Alzheimer's disease and prostate cancer.

When We Talk About Genes

Joan Stoler knows well the complexity of translating genetic information to the layperson. For years, Stoler, an HMS assistant professor of pediatrics at Boston Children's Hospital and program director of the Harvard Medical School Genetics Training Program, has been working with patients and families as they wrestle with the fact that they carry a potentially troublesome genetic mutation.

One problem she and others in her profession confront is that for many conditions there is no definitive test. The binary precision of the genetic condition found in the family Thakuria was counseling isn't the norm. What's more, if genomic information has been increasing by an order of magnitude each year, so has our appreciation of a gene's complexity. Sure, a gene may be turned on or off—but it may also simply be dimmed. Or the gene itself might be fine but one of its regulators may have gone rogue. For unknown reasons, a genetic alteration that may result in a calamitous deformity in one person might cause a physiological blip in another.

In other words, as our knowledge increases, the one gene-one protein pedagogy becomes almost quaint.

Stoler, however, must explain the subtleties we do know about to her patients, finding ways to bridge the knowledge gap, and, often, a cultural gap.

"For a couple from China, who often have only one child, learning of a genetic defect is a tremendous blow," she says. "One mother, from Central America, thought the mutation her child carried occurred because when she was pregnant she wore red during an eclipse. Some blame coffee. Part of my job is simply to educate patients about what this all means. I try to drive home that each of us has something that we can pass down to our children."

Stoler often finds herself trying to explain the basic concepts of cells, chromosomes, genes, and proteins through an interpreter. In these situations, she goes visual, using charts, drawings, tic-tac-toe boards, and whatever analogies she can to inform those she is working with.

In a way, experts like Stoler play the traditional role of gatekeeper. They collect and interpret the genetic data, and then decide the best methods for educating the patient. But as genetic testing becomes increasingly democratized, how will the role of gatekeepers shift?

Green's Genes

Robert Green is an expert in moving genetic discoveries into genomic medicine. He has investigated and deciphered the nuances of many genomes, including his own.

Like Thakuria and Stoler, Green, an HMS associate professor of medicine at Brigham and Women's Hospital and director of the G2P (genomes2people) research program, is a medical geneticist. In addition to treating patients, he oversees a research program that can best be described as translational genomics. Green and his research colleagues use sequencing technologies to diagnose some of the more obscure conditions. But Green's discipline is complicated by some hazy intricacies. To illustrate this, he references his own genetic blueprint.

A full sequence of Green's genes turns up a few million variations, 109,000 of which could initially be considered medically relevant. Of these, computational analysis predicts that approximately 11,900 have an effect on a protein. Further analysis to find the variations that are uncommon, and thus more predictive of disease, leaves only 1,800. When this remnant is processed through a database of known genetic diseases, only 16 rare mutations are left.

UPON REFLECTION: A full sequencing of Robert Green's genome revealed 16 mutations that, without the benefit of clinical context, could be considered alarming.

GRETCHEN ERTL/REDUX PICTURES/THE NEW YORK TIMES

Each of these 16 mutations could be alarming without clinical context. One of them, for example, is in the gene that causes Treacher Collins syndrome, a dominant condition resulting in severe facial deformities at birth. But here's the thing: Green doesn't exhibit a single feature of Treacher Collins. Which brings up yet another dilemma in the world of genetic diagnosis: There is no clear consensus on what defines a pathogenic mutation—and the race to package and sell translational software to patients and doctors may only add to the confusion.

"There's a powerful narrative in play that genomics will reveal all of our medical secrets, and that we all will benefit from genome sequencing," says Green. "But there are many questions to be answered before genomics is routine, particularly in healthy individuals. Can we validate the interpretation of disease risks so that we know what the genome is telling us? Will genetic information improve people's health? How often is it misunderstood? Can it be dangerous?"

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There is, in fact, a great deal of angst in the medical community about how an increasing glut of genetic information will affect patient behavior, and that is precisely what Green and his colleagues are studying.

Over the past decade Green has been the principal investigator for the REVEAL study: Risk Evaluation and Education for Alzheimer's Disease. For this project, researchers randomized participants to receive information regarding their genetic susceptibility to Alzheimer's.

"The study was run just like a clinical trial, except the drug we dispensed was genetic information," says Green.

The group measured potential patient harm in terms of anxiety, depression, and distress, eventually publishing in the *New England Journal of Medicine* that participants experienced a minimal and temporary rise in distress when they learned they were at an increased risk for Alzheimer's disease. Some of their subsequent behaviors were positive, such as better diet and more exercise; other behaviors were debatable, such as purchasing unregulated dietary supplements online. One striking finding: participants who learned that they were at increased risk reported increasing their long-term care insurance coverage.

For another set of participants, however, Green disclosed risk for heart disease along with the Alzheimer's risk and found that when people learned they were at risk for both conditions, they were, counterintuitively, less distressed.

"Our preliminary data suggest that learning about multiple risks, particularly if one of them seems preventable, is actually less distressing," he says.

In a separate study, Green and his group surveyed roughly 1,800 individuals who had received medically relevant genetic information through a direct-to-consumer company. When asked who they would present this information to, the respondents indicated overwhelmingly that they planned on discussing it with friends, family, and colleagues, and, in some cases, their family doctor. But few planned to discuss their results with a genetic specialist.

"As genomics enters the mainstream of medicine and society, regular physicians will have to learn to cope with this information about their patients," says Green. "Genetics is becoming democratized in a big way."

Green's newest studies are NIH-supported ones that will explore genomic sequencing in the medical care of adults and in newborns. Ultimately, this work anticipates a future where genomics data are available for every clinical visit.

Until then, medical geneticists are in the trenches with families excavating the uncertainties of inherited disease. Thakuria has continued to follow his family of patients. The good news is that, since availing themselves of genetic testing, no one in the family has died from the condition: screening and medical intervention has fended off what once seemed certain.

The kind of detailed sequencing that improved the family's options, however, is still reserved for extreme abnormalities. Thakuria, however, thinks that one day genomic sequencing will become a preventive measure, like mammograms and colonoscopies. If that occurs, family discussions of the results of genetic testing may lose some of their emotional freight. Then again, given family dynamics, maybe not. ■

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