A Picture of You

There's a lot to learn from the human genome. Genetic screening is our window in

by

ALICE PARK

IT ISN'T HARD TO SEE THE APPEAL OF GENOME screening. Our DNA, after all, is our blueprint, a biological schematic that dictates the shape of our cheekbones, whether we sneeze and wheeze every spring when the pollen pops, how resilient we are to mental challenges, and whether we'll succumb to heart disease, cancer or Alzheimer's. But although our genome is our molecular map, to think of the features it describes in the same way as the unmoving highways, bridges and ramps printed on a road atlas would be to vastly underestimate its relevance. Think instead of the genome as more of an adjustable touchscreen—embedded with certain operations but also ever-evolving, dependent on how we, and the environment, interact with it. The dynamic nature of DNA makes it a fascinating subject of study. It also makes it frustratingly difficult to interpret.

SOURCE CODES *Broad Institute labs lined with genome-sequencing equipment*

"When people talk about decoding the genome, I don't think it's the right metaphor," says David Altshuler, a geneticist and chief academic officer at the Broad Institute of Harvard and MIT. "*Decoding* implies that there is a code and that now we know what it means. Actually, what we've learned to do is to be very good at writing down the genome."

To be fair, that faithful transcription has given us quite a bit to work with. We know there are 20,000 or so genes, sections of the genome that carry instructions to make proteins that then create our blood cells, nerve cells, kidney cells, every cell. We know that genes make up only about 1% of the genome and that the rest harbors equally important commands for turning those genes on and off at the right time and in the right cells. And we know that all of it together makes up a string of 6 billion nucleotide bases, paired up like dance partners and entwined in a double-helical strand that is twisted into 23 pairs of chromosomes and packed into every one of our cells.

What we don't know yet is how these genes, and their genetic commanders in the DNA, operate in tandem to encode the exquisitely complex result that is the human body. It's as if we have the highways and the bridges and the buildings but not the civic engineer who can explain to us how they connect—in the right way, in the right places, in the right order.

So what's taking so long? It's been more than a decade since the Human Genome Project laid out a complete picture of our DNA. By now, the genome was supposed to have revealed, like some biological crystal ball, the mysteries of disease, dropping critical clues for new treatments and even cures in the process. That has happened to some extent, and it continues to happen, if more slowly than researchers committed to the task anticipated. Along the way, their appreciation for what the genome can help us do has grown deeper. "The prediction stuff, I think, is just a small part of how genomics is positively impacting medicine," says Altshuler. "The reason we study the genetics of diabetes is not just to predict who will get it, but to try to understand why people get it—to look at the group of people with the disease, compare them to people without the disease and understand how the genetic variants we find in the first group ultimately affect the disease."

While the early efforts to understand the genome were focused on the individual—say, on trying to develop personalized therapies tailored to a particular genetic makeup—those represent only one route to unlocking the power of the information contained within. More tantalizing is what happens when thousands of genomes are analyzed as a set, to find traits they share

and places where they differ. These are the patterns that scientists hope will help explain who responds to which medications, why some people draw the numbers in the hard-luck lottery of disease and which fortunate few are able to shake off some common ailments.

GENOME 2.0

There's no denying that what we've learned so far from our DNA has already begun to transform our understanding of certain diseases—cystic fibrosis, for example—and pointed to innovative ways of treating them. That genetic know-how has come from a variety of strategies, primarily genome sequencing, that are now commonplace even though they seemed forbiddingly out of reach not long ago. The first human genome sequencing took nine months and nearly $100 million to complete. Today, sequencing companies do the same analysis for around $1,000 and in a few days. Such analysis has enabled researchers to mine the richest possible resource for understanding human health. Using high-throughput computing power, these companies "read" in a bit of saliva or a drop of blood all 3 billion base pairs that make up a person's entire genetic code (in the case of whole-genome sequencing) or home in on just the genes (with exome sequencing). Either way, the printout is valuable data for genetic researchers and patients alike.

By comparing the sequences from people affected by diabetes, for instance, with those of people who don't have the condition, scientists can begin to expose the genetic culprits that may be contributing to the disease. A person's genome can also help doctors predict which patients will respond best to certain drugs and if they will develop adverse reactions to them, so physicians can fine-tune dosing and make existing drug treatments more effective. "That's one clear win right now for using genetic sequencing information," says Lisa Brooks, director of the genetic variation program at the National Human Genome Research Institute.

Mapping out people's DNA has revealed an estimated 10,000 disorders that are directly caused by mutations in a single gene, such as Huntington's, hemophilia and Tay-Sachs. Others, like sickle-cell anemia and cystic fibrosis, result from a single misplaced letter in the DNA sequence. Gene alterations have also been strongly connected to cancer risk; the BRCA1 and BRCA2 mutations, for example, increase a woman's risk of developing breast cancer by up to 65% and ovarian cancer by 40%. Running a genetic test from a sample of bodily fluid can reveal if someone has these mutations and can expeditiously turn her toward treatments that can save her life.

Sequencing is becoming so inexpensive and accessible that it's relatively easy to find out what your genome contains. The trickier issue is interpreting what it means. For most health conditions, including the chronic ones that affect so many of us—heart problems, diabetes and Alzheimer's among them—the genetic contribution isn't so black and white. "Risk genes don't add up one variant at a time, so that one contributes a 5% higher risk and another contributes a 5% higher risk and together they make a 10% higher risk," says Brooks.

Here's what makes DNA such a devilish disease-predictor: not only are researchers still in the dark in many cases about which genes link to which diseases, but even if they were able to compile a complete list of, say, diabetes-related genes, they would then have to discern how those genes interact with one another to cause the body's poor sugar control. And even if they could wrestle that stubborn problem successfully, they would still have to factor in non-genetic contributors such as diet, exercise and other lifestyle habits that can affect how active those genes will be. There are just so many moving parts. "Who knows how all of these interact?" says Brooks. "We are getting information on the variants, but we don't have the whole integrated picture. We have a very long way to go to have a really comprehensive understanding of the genetic risk of various diseases."

Rather than a Rand McNally atlas, our genomes are more like touchscreens.

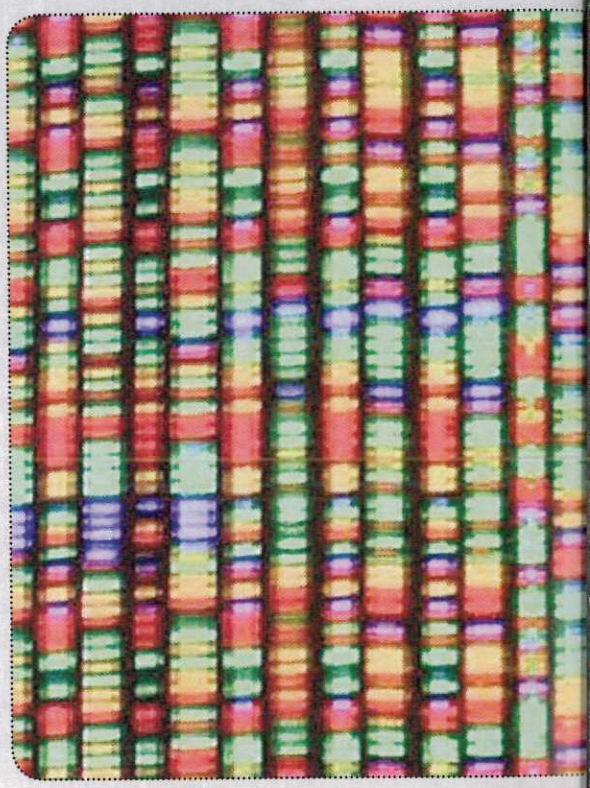
Which is why getting your genome sequenced—learning every letter in your DNA—won't tell you

How Do You Look in These Genes?

A full accounting of the human genome fills hundreds of volumes. Here are a few of its highlights

The gene known as **FOXE1** may contribute to **CLEFT LIP AND PALATE**

The **DRD4** and **DRD5** genes have been linked to **ADHD**



Do you have **RED HAIR?** Then you have two copies of a recessive gene on **CHROMOSOME 16** that controls melanin production. **FRECKLES** are linked to the same gene

CELIAC DISEASE has been associated with two genes located on **CHROMOSOME 6** that belong to a family called the leukocyte antigen (HLA) complex

TAY-SACHS, a rare inherited disorder most commonly found in Ashkenazi Jews, is caused by a mutation in the **HEXA** gene

In about 20% of **LUNG CANCER** cases, the patient is missing an anti-cancer gene known as **LKB1**

People with two copies of **CCR5-DELTA32** seem to be immune to **HIV INFECTION**

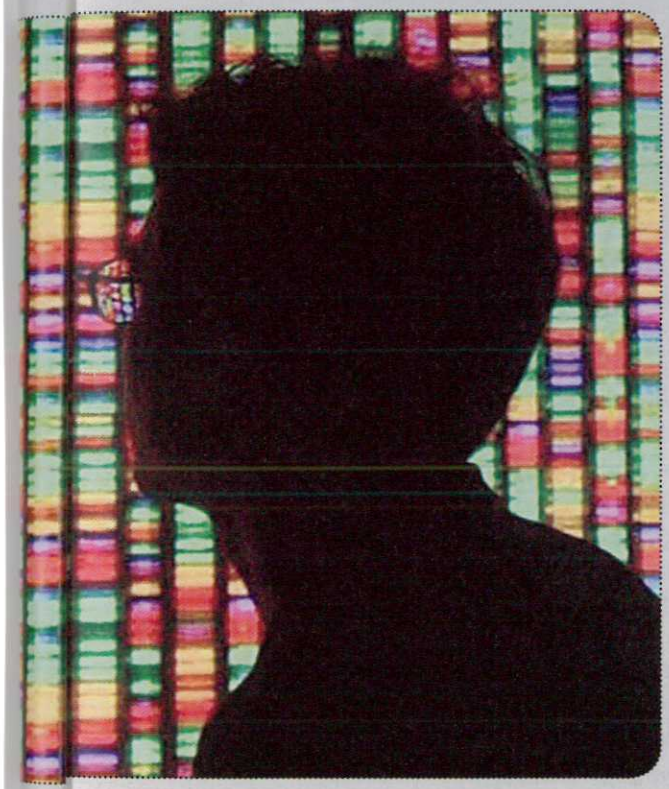
At least 18 mutations in the **SNCA** gene combine to cause **PARKINSON'S DISEASE**

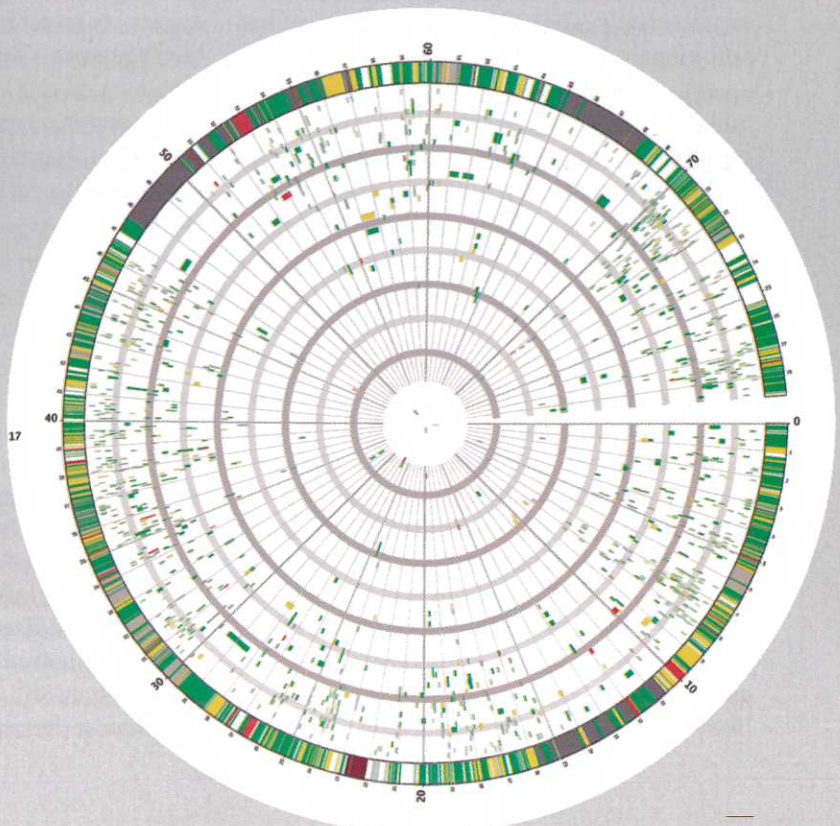
Studies note that people with a "strong tasters" phenylthiocarbamide **(PTC)** gene variant are less likely to smoke. Bonus: they are also **FITTER**, in part because of a genetic aversion to the taste of fatty foods

The most common inherited form of **HYPOTHYROIDISM** is a defect of the **TPO** (thyroid peroxidase) gene—on **CHROMOSOME 2**—which plays a role in thyroid hormone production

The **GPR126** gene influences a **PERSON'S HEIGHT AND TRUNK SIZE**

DTC-1, or adipose, is a gene associated with **OBESITY**. "It's like a thermostat," says Jonathan Graff, a professor at the University of Texas Southwestern Medical Center. "What version you have tells you how much weight you may gain"





DIFFERING VIEWS *Above: a visitor views a digital representation of the human genome at the American Museum of Natural History in New York. Right: a genetic map of human chromosome 17, in a circular array. The colored bands in the outer ring represent non-disease genes (green), cancer genes (red) and other disease genes (orange). Information within the circle subdivides the genes into those nucleotide sequences, or regions, in a gene that are expressed.*

much more today than it did in 2001, when the human genome was first mapped. While consumers overwhelmingly say they are interested in, and satisfied with, the DNA readouts they can get by sending samples of their spit to genome analysts, in more discriminating circles exactly what that information means remains a matter of hot debate. (The Food and Drug Administration is currently reviewing claims made by these consumer-screening companies and continues to prevent them from making causative claims in their marketing.)

Dozens of genes have been linked to diabetes, for example, but that doesn't mean a genome sequencing test that reveals the culpable altered forms necessarily indicates the disease's inevitability. "In the early days of the Human Genome Project, there was a little more of a sense that the genetic information would be more straightforward and, because of that, it would be easy to interpret," says Jean McEwen, the director of the Ethical, Legal and Social Implications Research Program at the National Human Genome Research Institute. "But the more we learn about the genome, the more we learn how complicated it is and how very little of it is straightforward."

The solution is to drill deeper. The government scientists who helped to sequence that first human genome are now multiplying their efforts exponentially. The 1000 Genomes Project has ambitiously sequenced the DNA of more than 2,500 people on its way to drawing a more detailed map of genes and genetic variants. So far, says Brooks, the researchers have identified 80 million sites where DNA differs. Back in 2001, that number was around 3,000. "We've clearly come a long way in our ability to look at genetic variants," Brooks says.

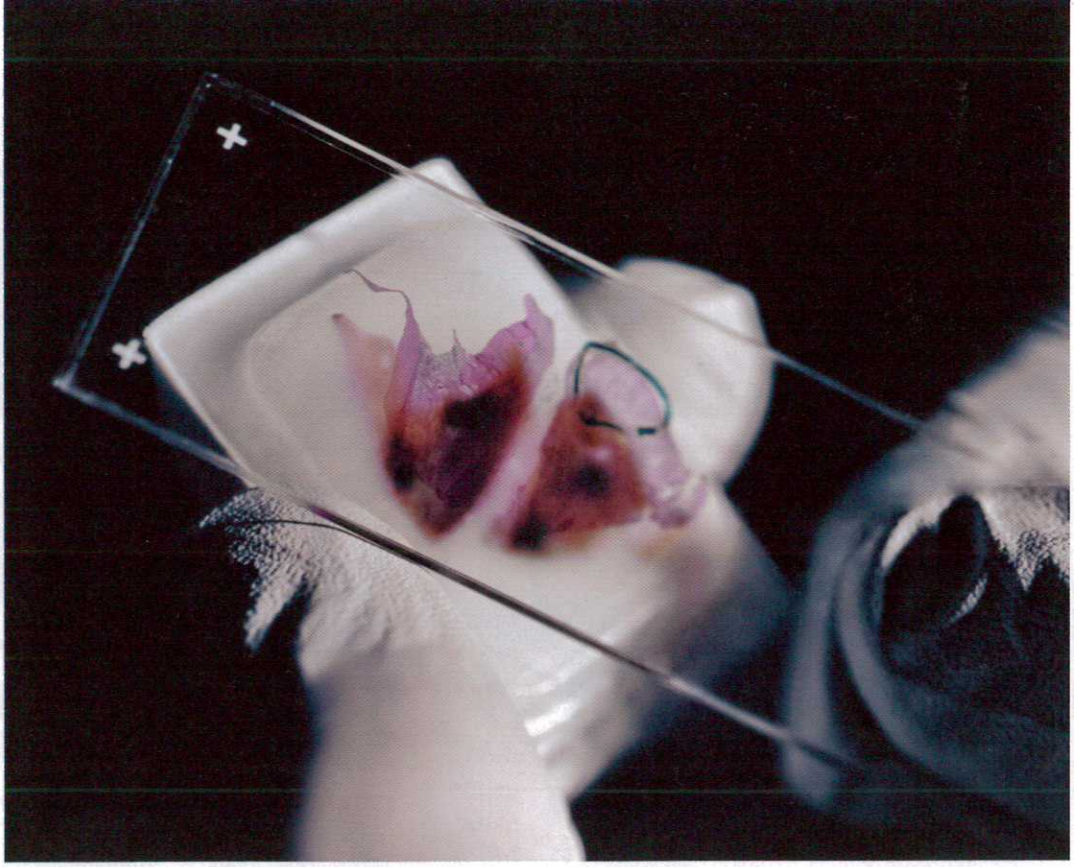
"The more we learn about the genome, the more we learn how complicated it is."

What will all those variants tell us? For one thing, isolating the most common genetic differences will help suss out the ones that are more likely to affect disease. And if not all of them prove to be directly relevant to understanding pathologies, some may still lead, like a molecular trail, to the genes that do. Comparing the genomes of people with and without specific conditions will also lay the foundation for building a hierarchy of "most wanted" genetic culprits. If a particular snippet of DNA appears most often among those with severe symptoms, for example, that sequence will become the focus of researchers, because it's likely to be responsible for driving the disease.

In another example of the power of genetic sequencing, after studying the genetic makeup of children with and without autism, scientists did not just pull out some genes that might be responsible for the developmental disorder; they also learned that kids with autism tend to have more added and deleted sections of DNA in their genomes than those who aren't affected. Investigating that pattern could lead to an understanding of where and why those changes occur and how they affect the proteins the genes make. And because the missing or additional bits of DNA aren't found in those without autism, they may also be affecting how neighboring genes function. That, in turn, could give researchers different ways to help the afflicted.

Such a window into the human condition may be more revealing than we bargained for, though, uncovering information that people don't expect—or aren't ready—to learn. Suppose a patient's genome is being combed for genes linked to breast-cancer risk and a geneticist stumbles upon mutations that boost the risk of Alzheimer's as well. Is she obligated to tell the patient? Or should she inform the patient only if there is an existing gene therapy to "treat" it?

For just such instances, genetic counselors have huddled with doctors to come up with categories of informed consent. At Columbia University, for instance, patients are given the option of being told about incidental findings only if a treatment is available for them. Similarly, they are asked if they want to be informed if genes that have been implicated in diseases turn up, even if doctors don't know how much those genes contribute to the condition. Still, admits Jill Goldman, a genetic counselor at the school, "there are so many differ-



TARGETED TREATMENT *A researcher prepares to remove a small bit of tumor tissue, marked by the blue circle, from a biopsy sample for DNA sequencing.*

ent scenarios, it's hard to expect people to really comprehend what they are hearing."

A CUE FROM CANCER

Maybe the best example of the promise of genomics, however, comes out of the research being done with cancer. Genetic information has modernized how we treat the disease, providing methods that cripple abnormal growth and prevent its spread. Cancer genomics has made its stand astride a relatively basic but powerful idea: that until now the tumor has been a forgotten player, dismissed in part because it was seen as an object only for elimination, but also out of ignorance. Scientists simply couldn't crack its secrets.

But like every other cell in the body, a tumor cell, which begins its life as a normal cell, contains a patient's entire genome. For whatever reason—an inherited genetic anomaly, tobacco exposure, too many years beneath the sun's ultraviolet rays—that genetic transcript is corrupted and goes rogue. Being able to sequence a tumor to uncover the mechanisms of its uncontrolled growth offers a promising, original slant for tackling cancer. "We like to call it a disruptive technology," says Matthew Ellis, a professor of medicine at Washington University in St. Louis and a leader in the sequencing of cancer-cell DNA. "Once we translate this technology into the clinical setting, it will completely rewrite the textbook on cancer, because we can start to fundamentally understand each patient's cancer genome and design treatments to match that information."

Toward that end, the National Institutes of Health began sequencing tumors from a variety of cancers in 2007. The mission of the Cancer Genome Atlas is to sequence dozens of types, about 500 samples of each. "The aim of the Human Genome Project was to provide a catalog of genes in the human genome. The atlas is building a catalog of the things that go wrong specifically in cancer," explains Paul Spellman, formerly of the NIH's National Cancer Institute and now at Oregon Health & Science University.

That catalog will join the findings of the 1000 Genomes Project and other like-minded DNA-data-collating programs as valuable resources that will bring us closer to fully understanding what the 6 billion letters of the human genome actually mean. Will we ever finally—actually—decode it? Maybe it doesn't matter. Even if much of our DNA dossier remains indecipherable, genomics might still one day be the cornerstone of nearly everyone's medical care. As Green says, "You don't have to be a pioneer to use it anymore." You just have to know how to read the map.

SCREEN TESTS

A rundown of what works and what doesn't

by ALEXANDRA SIFFERLIN

Breast and ovarian cancer

THE RISK

Women who carry a BRCA1 or BRCA2 mutation have a significantly higher risk of breast and ovarian cancer than the general population. (Men who carry the genes are at risk too, though less so than women.) Because the risk is so great and the danger considerable, those with the genes sometimes opt for preemptive, if decisive, surgery to remove their breasts or ovaries.

IS IT WORTH IT?

Both men and women who come from families with histories of these cancers should consider screening, since the chance of passing on the gene from generation to generation is 50%. Ashkenazi Jews, in particular, are likely carriers. Early testing is not necessary, however. The risk of developing these cancers in childhood is low.

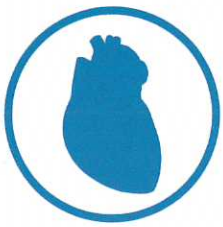
Colon cancer

THE RISK

A small percentage of colon cancers are caused by genetic mutations. For instance, about 3% of cases result from an inherited condition called Lynch syndrome. Those who have it are at significantly higher risk for colon cancer, and at a younger age. Similarly, familial adenomatous polyposis, another inherited disorder, produces polyps in the colon lining and puts patients at almost a 100% chance of developing cancer before age 40. No surprise, then, that some carriers of these mutations consider having their colon removed to lower the risk.

IS IT WORTH IT?

People with early-onset colon cancer—that is, those sufferers who are under 50 years old—or with 10 or more colon polyps over a lifetime or a family history of colon cancer (kids have a 50-50 chance of inheriting it) may want to consider genetic testing to determine future treatment and screening schedules. Depending on the genes involved, they could also be at risk for cancers of the ovaries, uterus or stomach.



Heart disease

THE RISK

There are screens to identify genes linked to an increased risk of arrhythmias and others to identify genes linked to cardiomyopathies—a thickening of the heart muscle—both of which raise the likelihood of cardiac arrest.

IS IT WORTH IT?

Patients with cardiomyopathy or an irregular heartbeat that cannot otherwise be explained can certainly undergo testing to see if the condition is genetically based. And genetic testing can help determine the best treatment for a patient given his or her risk. But there are many versions of heart disease, and most of them don't require testing.

Cystic fibrosis

THE RISK

Cystic fibrosis is a life-threatening disease characterized by a mucus buildup in the lungs, stomach and intestines that impedes both breathing and digestion. A pair of mutations in the CFTR gene are the cause, affecting a protein that regulates the transfer of salt through cells. People with both mutations will almost certainly have the disease, although its severity will differ based on those mutations.

IS IT WORTH IT?

Because both mutations must be present for cystic fibrosis to develop, the screening process often goes like this: pregnant mother is tested, and if she carries an offending gene, her partner is too. The significant risk of developing the disorder combined with a lack of long-term treatments argues for this test being seriously considered by prospective parents, particularly those of Northern European descent or with a family history of CF. Both are more likely to be carriers.

GENETIC TESTING CAN BE A ONE-STOP PROPOSITION, WITH A SINGLE SAMPLE OFFERING many insights. But just because you can be tested doesn't mean you should. Here are some common screenings, and our thoughts on whether each is worth getting. Consider it only a guide, though. The National Society of Genetic Counselors suggests seeing a counselor before making a decision that could have such serious repercussions for you and your family.

Sickle-cell disease

THE RISK

This red-blood-cell disorder—the result of mutations in the beta-globin gene—causes enervating anemia, blocking blood flow to the limbs and internal organs, which triggers pain and raises the risk of infection. It is inherited from both parents, one gene mutation from each. If both carry the trait, their child has a 25% chance of being affected.

IS IT WORTH IT?

A bone-marrow transplant is the only cure for sickle cell. So the U.S. Preventive Services Task Force recommends that all newborns are tested. Affected families can undergo preventive treatment. More to the point, prenatal screening makes good sense, particularly for those of African ancestry, who are much more susceptible; 1 in 400 carry the disease. People with a family history, too, may have a higher risk of carrying the mutation. Although diagnoses can be made with a routine blood test, genetic testing is recommended for confirmation.

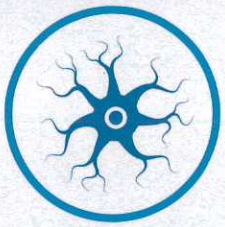
Fragile X syndrome

THE RISK

Fragile X syndrome is a genetic condition that results in a variety of developmental issues, including intellectual disabilities and autism-like features. The disorder, which tends to affect males more severely than females, is caused by mutations in the FMR1 gene that interfere with the synapses in nerve cells. It is inherited from the mother, at a prevalence of 1 in 4,000 males and 1 in 8,000 females.

IS IT WORTH IT?

Women with a family history of fragile X may want to consider screening to see if they are a carrier so they are aware of their risk of passing it on. People with developmental delays, learning disabilities or autism might also benefit from being tested, because those conditions have at times been associated with fragile X.



Spinal muscular atrophy

THE RISK

Spinal muscular atrophy (SMA) is a serious condition caused by mutations in the SMN1 gene that harm nerves in charge of voluntary muscle movement, interfering with head and neck control—including breathing and swallowing—as well as walking. Symptoms can appear before a child is 2 but also may not show until adulthood. There is currently no cure or treatment for SMA, which has an incidence rate of between 1 in 6,000 and 1 in 10,000.

IS IT WORTH IT?

The American College of Medical Genetics recommends carrier screening for SMA in early pregnancy or, better yet, before a child is conceived. As in sickle cell, both parents need to be carriers, and if they are there is a 25% chance they will produce an affected child. In addition, those with a family history of the disease may be more likely to be carriers.

Down syndrome

THE RISK

One of the most common genetic abnormalities, with an incidence rate of about 1 in 691, Down syndrome is the result of an extra copy of chromosome 21. Because non-invasive prenatal testing is now available for the developmental disorder—it was more invasive in the past—it no longer poses a risk to the pregnancy. The blood test, which analyzes fetal and placental DNA in the mother's blood, can detect up to 99% of cases of Down syndrome in utero.

IS IT WORTH IT?

All women can have a baby with a chromosomal abnormality, but generally the risk increases with maternal age. So women over 35 might want to take a harder look at Down screening. Families, of course, have to weigh the implications of finding out this information, including the decisions that it may entail.