Google cofounder SERGEY BRIN has a 50 percent chance of developing Parkinson's. It's coded in his DNA. So he's pushing for a new kind of science—heavy on the data—to find a cure before the disease finds him.

ILLUSTRATION BY RAFA JENN
after a day's work at Google headquarters in Mountain View, California, Sergey Brin drives up the road to a local pool. There, he changes into swim trunks, steps out on a 3-meter springboard, looks at the water below, and dives. & Brin is competent at all four types of springboard diving—forward, back, reverse, and inward. Recently, he's been working on his twists, which have been something of a struggle. But overall, he's not bad; in 2006 he competed in the master's division world championships. (He's quick to point out he placed sixth out of six in his event.) & The diving is the sort of challenge that Brin, who has also dabbled in yoga, gymnastics, and acrobatics, is drawn to: equal parts physical and mental exertion. "The dive itself is brief but intense," he says. "You push off really hard and then have to twist right away. It does get your heart rate going." & There's another benefit as well: With every dive, Brin gains a little bit of leverage—leverage against a risk, looming somewhere out there, that someday he may develop the neurodegenerative disorder Parkinson's disease. Buried deep within each cell in Brin's body—in a gene called LRRK2, which sits on the 12th chromosome—is a genetic mutation that has been associated with higher rates of Parkinson's. & Not everyone with Parkinson's has an LRRK2 mutation; nor will everyone with the mutation get the disease. But it does increase the chance that Parkinson's will emerge sometime in the carrier's life to between 30 and 75 percent. (By comparison, the risk for an average American is about 1 percent.) Brin himself splits the difference and figures his DNA gives him about 50-50 odds.

That's where exercise comes in. Parkinson's is a poorly understood disease, but research has associated a handful of behaviors with lower rates of disease, starting with exercise. One study found that young men who work out have a 60 percent lower risk. Coffee, likewise, has been linked to a reduced risk. For a time, Brin drank a cup or two a day, but he can't stand the taste of the stuff, so he switched to green tea. ("Most researchers think it's the caffeine, though they don't know for sure," he says.) Cigarette smokers also seem to have a lower chance of developing Parkinson's, but Brin has not opted to take up the habit. With every pool workout and every cup of tea, he hopes to diminish his odds, to adjust his algorithm by counteracting his DNA with environmental factors.

"This is all off the cuff," he says, "but let's say that based on diet, exercise, and so forth, I can get my risk down by half, to about 25 percent." The steady progress of neuroscience, Brin figures, will cut his risk by another half—bringing his overall chance of getting Parkinson's to about 13 percent. It's all guesswork, mind you, but the way he delivers the numbers and explains his rationale, he is utterly convincing.

Brin, of course, is no ordinary 36-year-old. As half of the duo that founded Google, he's worth about $15 billion. That bounty provides additional leverage. Since learning that he carries an LRRK2 mutation, Brin has contributed some $50 million to Parkinson's research, enough, he figures, to "really move the needle." It's light of the uptick in research into drug treatments and possible cures, Brin adjusts his overall risk again, down to "somewhere under 10 per-
That's still 10 times the average, but it goes a long way to counterbalancing his genetic predisposition.

It sounds so pragmatic, so obvious, that you can almost miss a striking fact: Many philanthropists have funded research into diseases they themselves have been diagnosed with. But Brin is likely the first who, based on a genetic test, began funding scientific research in the hope of escaping a disease in the first place.

His approach is notable for another reason. This isn't just another variation on venture philanthropy—the voguish application of business school practices to scientific research. Brin is after a different kind of science altogether. Most Parkinson's research, like much of medical research, relies on the classic scientific method: hypothesis, analysis, peer review, publication. Brin proposes a different approach, one driven by computational muscle and staggering large data sets. It's a method that draws on his algorithmic sensibility—and Google's storied faith in computing power—with the aim of accelerating the pace and increasing the potential of scientific research. "Generally the pace of medical research is glacial compared to what I'm used to in the Internet," Brin says. "We could be looking lots of places and collecting lots of information. And if we see a pattern, that could lead somewhere."

In other words, Brin is proposing to bypass centuries of scientific epistemology in favor of a more Googley kind of science. He wants to collect data first, then hypothesize, and then find the patterns that lead to answers. And he has the money and the algorithms to do it.
BRIN’S FAITH IN THE POWER
of numbers—and the power of knowl-
edge, more generally—is likely some-
thing he inherited from his parents,
both scientists. His father, Michael,
is a second-generation mathemat-
cian; his mother, Eugenia, is trained
in applied mathematics and spent
years doing meteorology research
at NASA. The family emigrated from
Russia when Brin was 6. At 17, he took
up mathematics himself at the Uni-
versity of Maryland, later adding a
second major in computer science.
When he reached Stanford for his
PhD—a degree he still hasn’t earned,
much to his parents’ chagrin—he
focused on data mining. That’s when
he began thinking about the power of
large data sets and what might come
of analyzing them for unexpected
patterns and insights.

Around the same time, in 1996,
Brin’s mother started to feel some
numbness in her hands. The initial
diagnosis was repetitive stress injury,
brught on by years of working at a
computer. When tests couldn’t con-
firm that diagnosis, her doctors were
stumped. Soon, though, Eugenia’s left leg
started to drag. “It was just the same as
my aunt, who had Parkinson’s years ago,”
she recalls. “The symptoms started in the
same way, at the same age. To me, at least,
it was obvious there was a connection.”
At the time, scientific opinion held that
Parkinson’s was not hereditary, so Brin didn’t
understand his mother’s concern. “I thought
it was crazy and completely irrational,” he
says. After further tests at Johns Hopkins
and the Mayo Clinic, though, she was diag-
nosed with Parkinson’s in 1999.
Even after the LRRK2 connection was
made in 2004, Brin still didn’t connect his
mother’s Parkinson’s to his own health.
Then, in 2006, his wife-to-be, Anne Wojcicki,
started the personal genetics company
23andMe (Google is an investor). As an
alpha tester, Brin had the chance to get an
early look at his genome. He didn’t find much
of concern. But then Wojcicki suggested he
look up a spot known as G2019S—the notch
on the LRRK2 gene where an adenine nucleo-
tide, the A in the ACTG code of DNA, some-
times substitutes for a guanine nucleotide,
the G. And there it was: He had the muta-
Given what seems like very bad news, most of us would actually do what Brin did: Go over our options, get some advice, and move on with life.

tion. His mother’s 23andMe readout showed that she had it, too.

Brin didn’t panic; for one thing, his mother’s experience with the disease has been reassuring. “She still goes skiing,” he says. “She’s not in a wheelchair.” Instead, he spent several months mulling over the results. He began to consult experts, starting with scientists at the Michael J. Fox Foundation and at the Parkinson’s Institute, which is not far from Google’s headquarters. He quickly realized it was going to be impractical to keep his risk from the public. “I can’t talk to 1,000 people in secret,” he says. “So I might as well put it out there to the world. It seemed like information that was worthy of sharing and might even be interesting.”

So one day in September 2008, Brin started a blog. His first post was called simply “LRKK2.”

“I know early in my life something I was substantially predisposed to,” Brin wrote. “I now have the opportunity to adjust my life to reduce those odds (e.g., there is evidence that exercise may be protective against Parkinson’s). I also have the opportunity to perform and support research into this disease long before it may affect me. And, regardless of my own health, it can help my family members as well as others.”

Brin continued: “I feel fortunate to be in this position. Until the fountain of youth is discovered, all of us will have some conditions in our old age, only we don’t know what they will be. I have a better guess than almost anyone else for what ills may be mine—and I have decades to prepare for it.”

In a sense, we’ve been using genetics to foretell disease risk forever. When we talk about “family history,” we’re largely talking about DNA, about how our parents’ health might hint at our own. A genetic scan is just a more modern way to link our familial past with our potential future. But there’s something about the precision of a DNA test that can make people believe that chemistry is destiny—that it holds dark, implacable secrets. This is why genetic information is sometimes described as “toxic knowledge.” Giving people direct access to their genetic information, in the words of Stanford bioethicist Hank Greely, is out and out “reckless.”

It’s true that in the early days of the science, genetic testing meant learning about a dreaded degenerative disease like Huntington’s or cystic fibrosis. But these diseases, although easy to identify, are extremely rare. Newer research has shown that when it comes to getting sick, a genetic predisposition is usually just one factor. The vast majority of conditions are also influenced by environment and day-to-day habits, areas where we can actually take some action.

But, surprisingly, the concept of genetic information as toxic has persisted, possibly because it presumes that people aren’t equipped to learn about themselves. But research shows this presumption to be unfounded. In 2009, The New England Journal of Medicine published results of the Risk Evaluation and Education for Alzheimer’s Disease study, an 11-year project that sought to examine how people react to finding out that they have a genetic risk for Alzheimer’s. Like Parkinson’s, Alzheimer’s is a neurodegenerative condition centered on the brain. But unlike Parkinson’s, Alzheimer’s has no known treatment. So learning you have a genetic predisposition should be especially toxic.

In the study, a team of researchers led by Robert Green, a neurologist and geneticist at Boston University, contacted adults who had a parent with Alzheimer’s and asked them to be tested for a variation in a gene known as ApoE. Depending on the variation, an ApoE mutation can increase a person’s risk for Alzheimer’s from three to 15 times the average. One hundred sixty-two adults agreed; 53 were told they had the mutation.

The results were delivered to the participants with great care: A genetic counselor walked each individual through the data, and all the subjects had follow-up appointments with the counselor. Therapists were also on call. “People were predicting catastrophic reactions,” Green recalls. “Depression, suicide, quitting their jobs, abandoning their families. They were anticipating the worst.”

But that isn’t what happened. People told that they were at dramatically higher risk for developing Alzheimer’s later in life seemed to process the information and integrate it into their lives, often choosing to lead more healthy lifestyles. “People are handling it,” Green says. “It doesn’t seem to be producing any clinically apparent distress.”

In other experiments, Green has further challenged the conventional wisdom about the toxicity of genetic information: He has begun questioning the need for counselors and therapists. “We’re looking at what happens if you don’t do this elaborate thing. What if you do it like a lab test in your doctor’s office? We’re treating it more like cholesterol and less like Huntington’s disease.”

In other words, given what seems like very bad news, most of us would do what Sergey Brin did: Go over our options, get some advice, and move on with life. “Everyone’s got their challenges; everyone’s got something to deal with,” Brin says. “This is mine. To me, it’s just one of any number of things that I could get in old age. And the most important factor is that I can do something about it.”

**IF BRIN’S BLOG POST BETRAYED** little fear about his risk for Parkinson’s, it did show a hint of disappointment with the state of knowledge on the disease. (His critique was characteristically precise: “Studies tend to have small samples with various selection biases.”)

His frustration is well founded. For decades, Parkinson’s research has been a poor cousin to the study of Alzheimer’s, which affects 10 times as many Americans and is therefore much more in the public eye. What is known about Parkinson’s has tended to emerge from observing patients in clinical practice, rather than from any sustained research. Nearly all cases are classified as idiopathic, meaning there’s no known cause. Technically, the disease is a result of the loss of brain cells that produce the neurotransmitter dopamine, but what causes those cells to die is unclear. The classic symptoms of
Why not do science differently?
Gather tons of data, then start searching for correlations.

the condition—tremors, rigidity, balance problems—come on gradually and typically don’t develop until dopamine production has declined by around 80 percent, meaning that a person can have the disease for years before experiencing the first symptom.

As far as treatments go, the drug levodopa, which converts to dopamine in the brain, remains the most effective. But the drug, developed in 1967, has significant side effects, including involuntary movements and confusion. Other interventions, like deep-brain stimulation, are invasive and expensive. Stem cell treatments, which generated great attention and promise a decade ago, “didn’t really work,” says William Langston, director of the Parkinson’s Institute. “Transferring nerve cells into the brain and repairing the brain has been harder than anybody thought.”

There are, however, some areas of promise—including the 2004 discovery of the LRRK2 connection. It’s especially common among people of Ashkenazi descent, like Brin, and appears in just about 1 percent of Parkinson’s patients. Rare as the mutation is, however, LRRK2 cases of Parkinson’s appear indistinguishable from other cases, making LRRK2 a potential window onto the disease in general.

LRRK2 stands for leucine-rich repeat kinase. Kinases are enzymes that activate proteins in cells, making them critical to cell growth and death. In cancer, aberrant kinases are known to contribute to tumor growth. That makes them a promising target for research. Drug companies have already developed kinase inhibitors for cancer; it’s a huge opportunity for Parkinson’s treatment, as well: If overactive kinases interfere with dopamine-producing cells in all Parkinson’s cases, then a kinase inhibitor may be able to help not just the LRRK2 carriers but all people with the disease.

Another promising area for research is that delay between the loss of dopamine-producing cells and the onset of symptoms. As it stands, this lag makes treatment a much more difficult problem. “By the time somebody has full-blown Parkinson’s, it’s way too late,” Langston says. “Any number of promising drugs have failed, perhaps because we’re getting in there so late.” But doctors can’t tell who should get drugs earlier, because patients are asymptomatic. If researchers could find biomarkers—telltale proteins or enzymes detected by, say, a blood or urine test—that were produced before symptoms emerged, a drug regimen could be started early enough to work.

And indeed, Brin has given money to both these areas of research, predominantly through gifts to the Parkinson’s Institute and to the Michael J. Fox Foundation, which is committed to what’s called translational research—getting therapies from researchers to the clinic as quickly as possible. Last January the Fox Foundation launched an international consortium of scientists working on LRRK2, with a mandate for collaboration, openness, and speed. “The goal is to get people to change their behavior and share information much more quickly and openly,” says Todd Sherer, head of the Fox Foundation’s research team. “We need to change the thinking.”

As Brin’s understanding of Parkinson’s grew, though, and as he talked with Wojcicki about research models, he realized that there was an even bolder experiment in the offing.

In 1899, scientists at Bayer unveiled aspirin, a drug it offered as an effective remedy for colds, lumbago, and toothaches, among other ills. How aspirin—or acetylsalicylic acid—actually worked was a mystery. All people knew was that it did (though a discouraging side effect, gastric bleeding, emerged in some people).

It wasn’t until the 1960s and ’70s that scientists started to understand the mechanism: Aspirin inhibits the production of chemicals in the body called prostaglandins, fatty acids that can cause inflammation and pain. That insight proved essential to understanding the later discovery, in 1988, that people who took aspirin every other day had remarkably reduced rates of heart attack—cases in men dropped by 44 percent. When the drug inhibits prostaglandins, it seems, it inhibits the formation of blood clots, as well—reducing the risk of heart attack.

The second coming of aspirin is considered one of the triumphs of contemporary medical research. But to Brin, who spoke of the drug in a talk at the Parkinson’s Institute last August, the story offers a different sort of lesson—one drawn from that period after the drug was introduced but before the link to heart disease was established. During those decades, Brin notes, surely “many millions or hundreds of millions of people who took aspirin had a variety of subsequent health benefits.” But the association with aspirin was overlooked, because nobody was watching the patients. “All that data was lost,” Brin said.

In Brin’s way of thinking, each of our lives is a potential contribution to scientific insight. We all go about our days, making choices, eating things, taking medications, doing things—generating what is inelegantly called data exhaust. A century ago, of course, it would have been impossible to actually capture this information, particularly without a specific hypothesis to guide a researcher in what to look for. Not so today. With contemporary computing power, that data can be tracked and analyzed. “Any experience that we have or drug that we may take, all those things are individual pieces of information,” Brin says. “Individually, they’re worthless, they’re anecdotal. But taken together they can be very powerful.”

In computer science, the process of mining such large data sets for useful associations is known as a market-basket analysis. Conventionally, it has been used to divine patterns in retail purchases. It’s how Amazon.com can tell you that “customers who bought X also bought Y.”

But a problem emerges as the data in a basket become less uniform. This was the focus of much of Brin’s work at Stanford, where he published several papers on the subject. One, from 1997, argued that given the right algorithms, meaningful associations can be drawn from all sorts of unconventional baskets—student enrollment in classes, word occurrence in text documents, users’ visits of Web pages, and many more.

It’s not a stretch to say that our experiences as patients might conceivably be the next item on the list.

This is especially true given the advances in computational power since 1997, when Brin and his fellow Stanford comp-sci student Larry Page were starting Google. “When Larry and I started the company,” Brin says, “we had to get... CONTINUED ON PAGE 138
HIGH-SPEED SCIENCE
Can a model fueled by data sets and computational power compete with the gold standard of research? Maybe. Here are two timelines—one from an esteemed traditional research project run by the NIH, the other from the 23andMe Parkinson's Genetics Initiative. They reached almost the same conclusion about a possible association between Gaucher's disease and Parkinson's disease, but the 23andMe project took a fraction of the time. —Rachel Swaby

TRADITIONAL MODEL
1. Hypothesis: An early study suggests that patients with Gaucher's disease (caused by a mutation to the GBA gene) might be at increased risk of Parkinson's.
2. Studies: Researchers conduct further studies, with varying statistical significance.
3. Data aggregation: Sixteen centers pool information on more than 5,500 Parkinson's patients.
4. Analysis: A statistician crunches the numbers.
5. Writing: A paper is drafted and approved by 64 authors.
7. Acceptance: NEJM accepts the paper.
8. Publication: The paper notes that people with Parkinson's are 5.4 times more likely to carry the GBA mutation.

TOTAL TIME ELAPSED: 6 YEARS

PARKINSON'S GENETICS INITIATIVE
1. Tool Construction: Survey designers build the questionnaire that patients will use to report symptoms.
2. Recruitment: The community is announced, with a goal of recruiting 10,000 subjects with Parkinson's.
3. Data aggregation: Community members get their DNA analyzed. They also fill out surveys.
4. Analysis: Reacting to the NEJM paper, 23andMe researchers run a database query based on 3,200 subjects. The results are returned in 20 minutes.
5. Presentation: The results are reported at a Royal Society of Medicine meeting in London. People with GBA are 5 times more likely to have Parkinson's, which is squarely in line with the NEJM paper. The finding will possibly be published at a later date.

TOTAL TIME ELAPSED: 8 MONTHS