CHAPTER 6

Will I pass this on to my children?

The Genetics of Alzheimer's—and Paths to Prevention

"Will our daughter get this?" Celia asked me, her brow furrowed with worry as she held hands with her 70-year-old husband, who sat quietly beside her.

I had just shared with them that Celia, a soft-spoken 69-year-old retired journalist, had rapidly progressive Alzheimer's, with mild memory and language impairment and good life skills. The three of us had agreed on a treatment plan, and now, as our meeting drew to a close, Celia fearfully asked the question that was troubling her most. I could see her husband tense up as she did so. Concerned as they were about this new and unplanned future of theirs, they were just as afraid for their daughter's.

"There is an increased risk to your daughter," I told them, "but it is a very small one. Given the type of Alzheimer's that you have, with some lifestyle modifications we can actually reduce your daughter's risk to even below that of someone who has no family history of it."

Their relief was almost palpable.

Like Celia, most patients with Alzheimer's worry about the genetic risks they may pass on to their children. Many are already feeling bad about the burden they pose to children because of their illness, and their guilt is compounded by a fear that their children might inherit the genes for Alzheimer's. Many children also worry about their own risk when a parent is diagnosed.

A Chapter Excerpt from

"The Spectrum of Hope: A New and Optimistic Approach to Alzheimer's and Other Dementias."

Gayatri Devi, MD

About 95 percent of all Alzheimer's cases are late-onset, with symptoms beginning after age 65, as Celia's had. Most of these cases are "sporadic," which means the disease is not inherited. This type of Alzheimer's is the focus of most of this book, and it is a multifactorial disease, meaning that many factors contribute to the development of the illness. Sixty percent of late-onset Alzheimer's can be prevented by controlling these factors—sometimes it's as simple as adopting a healthful diet, increasing physical activity, and becoming more socially engaged. Children of patients with late-onset Alzheimer's have only a small increased risk when compared with those without a family history of the disease.

Early-onset Alzheimer's, on the other hand, occurs when symptoms appear before age 65 and is much more genetically based and far harder to prevent with currently available preventive options. It constitutes only 5 percent of cases and is also most often sporadic—in other words, it's caused by a mutation in the patient's own genetic makeup, rather than one he or she inherited. However, the children of patients with early-onset Alzheimer's have a 50 percent chance of developing the disease.

Early-onset Alzheimer's occurs when symptoms appear before age 65 and is much more genetically based and far harder to prevent with currently available preventive options.

Early-onset Alzheimer's cases are also the most rapidly progressive on the Alzheimer's spectrum, although as we saw in Chapter 1 with Jonathan, who was diagnosed at 44 and is still living on his own at 64, this is not always true. Genetic influences are far stronger in such cases, and inheritance is in an "autosomal dominant" fashion, meaning that each child has a 50 percent chance of inheriting the disease from an affected parent. It is important to realize that it's possible—although improbable—for an affected parent to have four children who never develop the disease. Each child inherits the gene randomly, as with a coin flip. Of course it's possible that four coin tosses come up "heads," but it's statistically unlikely.

Early Onset: Theo's Story

Several types of genes lead to the various subtypes of early-onset Alzheimer's. That discussion is beyond the scope of this book, but I would like to talk about one exceptional family's early-onset story. Theo, Cindy, and Mike were three siblings at risk of developing Alzheimer's thanks to simple bad luck in life's genetic roulette.

At age 16, their mother, Patricia, fell in love with their father, Peter, a very handsome serviceman who had just returned from the Korean War. At the time, she was living in an orphanage, where she had been placed at the age of 3, after the death of her own mother. (It was the prevailing attitude of the time that fathers could not raise young children, particularly girls, on their own.)

Patricia and Peter married six months after they met, and they were such an arresting couple that they were featured on the cover of a national magazine. This was the happiest time of Patricia's life, and in the years after the marriage, she gave birth to their three children—Theo first, then Cindy, then Mike.

Within a few years, Peter's behavior became erratic. He developed a rapidly progressive dementia that doctors at the time believed was caused by Creutzfeldt-Jakob disease, popularly known as "mad cow" disease. By the time he was in his late thirties, Peter needed help with all daily life skills, including toileting. Raising three young children at the same time, Patricia had no choice but to place Peter in a nursing home. He remained there, mute and bed bound, for a remarkable twenty years until he died at the age of 59. Despite the pressures of raising her children alone, supported only by her job as a day care worker and Peter's government pension, Patricia visited him faithfully every week.

Patricia was effectively a single mother. At first, her little family thrived despite the difficult circumstances—her children grew up, and all seemed well in her world. Her eldest son, Theo, got married and moved away to start a family of his own, getting a job as a driver for a delivery company. But he began to develop behavioral problems at 29, just as his father had before him. Marina, Theo's wife, noticed that

Theo's rapidly progressive, early-onset Alzheimer's left him mute and incontinent within a few years of my diagnosis. Sadly I was not able to help him in any substantive way. Even so, I wanted to examine Cindy and obtain blood for genetic analysis. This was the youngest family in the world with the condition, and I wanted to investigate it as best as I could with the available tools. The results would add to the literature in the field, but I also hoped that we could help Theo's daughter, Molly, if she carried the culprit gene. It took some time and persuasion, but eventually, I earned Patricia's trust. I was able to get blood samples from not only Cindy and Mike, but also from the family of her husband, Peter. It took a great deal of research, but eventually we identified a unique mutation in both Cindy and Theo that had caused their early-onset Alzheimer's and that likely had taken their father from them.

Mike was the only sibling left without clinical signs of the illness. He had spent much of his young adult life acting as a caregiver to his affected siblings, and believed his fate was already etched in stone. Over the several years' span that I spent working with and researching this family, I had developed a fondness for this shy and caring young man. He barely spoke but was devoted to his siblings and his mother. Once in a while, I would get a glimpse of his dry humor and we would laugh together. Did Mike also possess the rogue gene that had wreaked such havoc on his family?

Mike was 29 when he got his results. He had been waiting for this dreaded illness to develop since he was 20. However, we happily discovered that Mike did *not*, in fact, have the mutation that would soon cause the premature deaths of his brother and sister, and I got to make one of the most memorable phone calls of my career. I was extremely excited to let him know the good news, expecting Mike to be relieved, thrilled, and thankful for the information.

Instead, I was met only with silence.

"Are you there, Mike?" I asked.

"Yes," Mike said nonchalantly. "So you are saying I don't have the gene . . ."

I remember being surprised, perhaps even a little hurt. What I had failed to consider was that Mike now had to figure out what to do with

the rest of his life. This was a life he hadn't thought he was going to live. Suddenly, he had to come to terms with what he could be without the disease. He was overwhelmed by the possibilities.

Cindy died first, at home with Patricia holding her as she took her last breath. Theo followed a few months later, four years after he had first sought treatment.

Eighteen years have passed since I made that phone call to Mike. I hope he has found happiness and a path in life. I know that wherever he is, he is not suffering from the tragic illness that took his father, his brother, and his sister from him. But when I look back on the case now, Patricia is the one who stands out for me. In many ways she personified motherhood and the face of love and resilience in the presence of overwhelming odds. She decided to speak to me, even though she hated doctors, because she wanted to figure out if there was anything that could be done to save her youngest son. Even though her experience gave new meaning to hard luck stories, she never complained, and she fought for her children with an awe-inspiring fierceness and determination. To this day, when I am feeling sorry for myself, I think of Patricia's strength and tell myself to snap out of it.

A Multifactorial Disease

As I mentioned earlier, late-onset Alzheimer's is determined by genetics only to a small degree. One thing that proves this is the fact that if one of a pair of identical twins develops late-onset Alzheimer's, it's statistically more likely that his or her twin will *not* get the condition than that he or she will. This would not occur with a disease that is determined solely by genetics. It is clear that later-life factors (in addition to early-life environment, which is usually similar in identical twins) contribute significantly to whether a person develops clinical evidence of late-onset Alzheimer's.

In 2011 the Alzheimer's Association and the National Institute of Health introduced the concept of preclinical Alzheimer's disease. People

THE GENETICS OF ALZHEIMER'S

Here is an overview of the modes of inheritance and major genes implicated in Alzheimer's.

LATE-ONSET ALZHEIMER'S

- Symptoms manifest after age 65
- Common—95 percent of all cases (of these, 5 percent inherited with family history of late-onset Alzheimer's; 95 percent sporadic—no family history)
- Multifactorial, with genetics playing a small role; 60 percent of cases are preventable
- Course varies dramatically from person to person—can be rapidly or slowly progressive
- Associated with the APOE4 allele of the APOE gene on chromosome 19

EARLY-ONSET ALZHEIMER'S

- Symptoms manifest before age 65
- Rare—5 percent of all cases (of these, 10–15 percent inherited with family history of early-onset Alzheimer's; 85–90 percent sporadic or with family history of late-onset Alzheimer's)
- Strongly genetic—50 percent of children will get the disease; cannot be prevented
- Usually rapidly progressive, although exceptions occur
- Seen with mutations in chromosomes 1, 14, and 21

diagnosed with this have all the biological markers—brain deposits and brain changes—seen with Alzheimer's, but no change in memory or cognition. This stage can last as long as two decades or more before any symptoms manifest. In fact, patients at this end of the Alzheimer's

spectrum may die at a ripe old age without ever developing symptoms. What protects them even as their identical twin brothers and sisters begin to show cognitive loss? What role does genetics play, and how can the environment alter a person's genetic inclinations? Although we don't yet have definitive answers to these questions, it is clear that mitigating risk factors and improving heart health and general fitness prevents many cases on the spectrum.

Understanding the Risk

I like to reassure patients and their families by giving them data from one of the largest studies I have ever done. I looked at more than 5,500 siblings and parents of patients with Alzheimer's alongside age-matched adults who did not have the disease. Presuming that everyone lived to 90 years of age, I found that those with a relative with Alzheimer's had about a one-in-four chance of developing late-onset Alzheimer's, whereas those without an afflicted relative had a one-in-five chance of doing so. In other words, if neither my parents nor my siblings have Alzheimer's (and I live to age 90), I still have a 20 percent chance of getting it. And my friend Kitty, whose mother had Alzheimer's, has a 26 percent chance.

It's worth noting that statistics can be presented in ways that make the odds sound more alarming. For example, in my study, we concluded that someone like Claire, whose mother had Alzheimer's, had a 50 percent increased risk (risk ratio of 1.5) for developing Alzheimer's when compared with someone like me (risk ratio of 1.0), once we had factored in variables that could contribute to the difference, like education.

Similarly, contrast the varying ways in which the statistical results of a large study of identical twins could be reported. The study followed 11,000 sets of twins over the age of 65. One way to report the results would be that 55 percent of one of a pair of identical twins did not develop Alzheimer's, and 45 percent did. Another way to report the results would be that genetic factors were responsible for 80 percent of

Alzheimer's cases. Although both these sets of statements are true, the take-home message from each is quite different.

Genetic Counseling

Despite these statistics, I can empathize with children of patients with Alzheimer's when they fear that they too will develop the disease. Although I do not have a first-degree relative with dementia, my mother had a chronic progressive neurologic condition that led to her death after a decade-long struggle. As I watched her grow ill, even as her spirit burned undiminished, I was inspired to explore all possible avenues to maintain her quality of life. In fact, she was the reason why I began to explore neuromodulation techniques like transcranial magnetic stimulation (TMS). Although it was too late for TMS to benefit my mother, I know she would be happy that it is benefiting others. I owe much of my drive and success to her, but my awareness of her illness also makes me worry whenever I have a minor fumble.

Every time I stumble or choke on water, a niggling part of my brain lights up with alarm. *Is this the first sign?* I think. I realize that we all stumble on uneven sidewalks. And I know that when one has a tendency to talk and drink at the same time, as I do, there may be occasional coughing spells. What's more, as a neurologist, I am aware that my risk of inheriting the genes of my mother's illness is minimal. But the brain is not a rational organ—at a deep, highly hardwired, and very primitive level it is ruled by emotion. Of course we forget things sometimes—in fact, we are wired to forget, just like we are wired to stumble or choke occasionally. But when there is a family history of Alzheimer's, ordinary acts of everyday forgetfulness acquire an ominousness that can be hard to shake.

When I meet patients for genetic counseling, I try to be sensitive to their fears, both rational and irrational. But I also tell them that they can do things that will actually reduce their risk for developing Alzheimer's to below that of their peers whose parents did not have the illness. In

addition to lifestyle, diet, amount of exercise, and conditions like high blood pressure and diabetes, one's level of educational and occupational engagement seem to make a difference. All these variables influence two key factors that ultimately determine the clinical presentation of Alzheimer's: brain reserve and cognitive reserve.

As I mentioned in earlier chapters, brain reserve is a physical measure of the number of brain cells. The larger the number of cells, the larger the brain is physically and the greater the brain reserve. Strokes and head injuries eat into brain reserve, reducing the number of cells. Cognitive reserve, on the other hand, measures the number of connections between nerve cells and the robustness of the brain circuits; in other words, it's about how much we use the brain we have.

Formal and informal education increase cognitive reserve, as do activities as disparate as Sudoku and fox-trotting, by increasing nerve cell sprouting and the connections between cells, much as a bare, dying tree bursts into lush life with the right mixture of soil, water, and weather. Our 80 billion–plus neuronal trees flourish and are kept strong by good blood flow and a healthy lifestyle, even in the face of disease. Inactivity and isolation reduce cognitive reserve, withering neuronal sprouts and weakening vital brain circuits. High blood pressure, diabetes, and heart disease can all lead to reduced brain blood flow, which has a negative impact on both brain reserve and cognitive reserve.

To avoid abnormal plaque pathology and stay on the preclinical end of the Alzheimer's spectrum in the event of such pathology, we need to safeguard brain reserve by protecting our brains from injury and increase cognitive reserve with lifestyle changes.

Xavier's Quest to Prevent Alzheimer's

"I'm worried that I'm becoming like my dad," said Xavier, a no-nonsense 50-year-old businessman and the son of one of my patients. "Like him, I find myself forgetting. I need to know if I am developing Alzheimer's so I can plan for the future. I also remember

you said that sixty percent of Alzheimer's like the type my father had can be prevented. We need to come up with a game plan."

I had met Xavier when he accompanied his father on a visit to my office the year before. I had diagnosed his dad with a mixed dementia arising from both Alzheimer's and small strokes.

"Don't get me wrong: I never had a good memory to begin with," Xavier continued. "I've never been good with names or faces, but lately it seems to have gotten a lot worse. The other day I blanked on my business partner's name, and we've been together for twelve years. I am concerned, especially given my dad's condition."

At the time, Xavier was experiencing other significant sources of stress as well. His adult son had recently been killed in a car accident, which had, naturally, been devastating. The loss had strained his relationship with his wife.

"Of course, this affects my overall state of mind. It's hard to concentrate, because I am so sad," he said. Furthermore, Xavier was overweight and had high blood pressure, high cholesterol, and chronic insomnia, sleeping only about five hours a night.

I had Xavier go through a testing protocol that evaluated all of his risk factors for dementia, specifically looking for factors that contribute to the disease that we could prevent. We checked his laboratory data for his cholesterol, diabetic risk, thyroid function, stroke risk indices, and genetic risk for Alzheimer's. Because his wife had complained about his excessive snoring, he underwent a sleep study. He had a brain MRI to look for potential problems with his brain circulation. He also underwent a neurocognitive evaluation, so we could get an accurate measurement of his brain's functional abilities and establish a baseline for future comparison.

The results of this thorough evaluation were exactly what we needed to get Xavier the tailored help he required to prevent Alzheimer's. His sleep study showed that he had sleep apnea, a condition that can be caused or worsened by weight gain. Patients with the condition stop breathing while sleeping, sometimes hundreds of times a night, for anywhere from a few seconds to a minute, and this temporarily deprives the brain of oxygen. I thought Xavier's sleep apnea was making his high

blood pressure, memory loss, and depression worse. He began wearing a special mask to bed, which allowed him to get several hours of uninterrupted sleep each night for the first time in years. Not only did this reduce his risk for developing Alzheimer's by helping to control his blood pressure and alleviating his depression, but wearing the mask also afforded him better-quality sleep, which further reduced his blood pressure and depression. His brain MRI revealed that he'd had a few small strokes. This surprised him but not me, because such small strokes are not uncommon in those with high cholesterol and hypertension. Like most patients, Xavier didn't even know he had had them, which unfortunately kept him from preventing new ones. These very small strokes, if allowed to increase in number over time, can eventually cause serious problems with thinking and mobility and may even lead to dementia, as was the case with Xavier's father. I told Xavier that controlling his hypertension and cholesterol was essential. Xavier began a heart-healthy, Mediterranean diet and started a program of forty-five minutes of aerobic exercise three times a week. In conjunction with his internist, I also optimized his medication regimen to make sure that his blood pressure and cholesterol were under control. All of this—better blood pressure and cholesterol control, prevention of more mini-strokes, a brain-healthy diet, and aerobic exercise—reduced his risk for Alzheimer's.

Small strokes, if allowed to increase in number over time, can eventually cause serious problems with thinking and mobility and may even lead to dementia.

His neurocognitive performance showed some mild memory loss and trouble with language, but I thought that was likely related to anxiety and stress rather than from pathology on the spectrum. He began taking an antidepressant under the supervision of a psychiatrist. Xavier was a type-A person—hypercompetitive and driven to succeed—and because he was a man in his fifties, this put him at risk for cardiac problems like heart attacks. I suggested he and his wife talk with a counselor to address the problems they were having over the loss of their son, and

encouraged him to begin some type of meditation or relaxation therapy. Reducing stress and anxiety is also important for keeping the brain healthy and functional.

Unable to embrace meditation—"I am just too hyper to relax like that, I guess"—Xavier took up running, which he found to be calming. It had the added benefit of increasing brain blood flow and getting Xavier in better shape, which is also helpful in preventing Alzheimer's. His genetic testing showed that he had one of the E4 variants of the APOE gene associated with a higher risk for developing Alzheimer's. I discussed this with Xavier, and it motivated him to be even more committed to his prevention strategies. I told Xavier that with the kind of modifications he had embraced, it was highly likely that we could prevent him from developing Alzheimer's. Even if he were to develop the brain pathology associated with Alzheimer's, he could remain at the preclinical end of the Alzheimer's spectrum without functional problems.

Ideally, women and men should have neurocognitive baselines established at age 50, just as we have baseline bone densities and colonoscopies.

Xavier has done well in the years since we instituted his prevention regimen. He is back at his college weight, and in fact he says he is in better shape than he was then. He has become fit enough that his sleep apnea resolved and he no longer needs a sleep mask. As his fitness improved and his sleep apnea disappeared, his blood pressure normalized and he was able to stop taking those medications.

Xavier is a success story for many reasons, but especially because he had the courage to challenge what he thought was an unchangeable destiny.

Although he was proactive about assessing his risk for dementia, his approach was atypical. More often than not, children of patients with dementia worry about developing it but don't do anything to try to prevent it. I think the fear of a diagnosis as well as an assumption that the condition can't be prevented keeps them from making an appointment, but such fear is misplaced, as we saw with Xavier. Inheriting Alzheimer's

is not as inevitable as many patients and their families seem to think—especially when prevention strategies are employed. It's thought that about 60 percent of all late-onset Alzheimer's cases are actually preventable with widely available therapies and relatively simple lifestyle modifications.

Because so many modifiable elements go into the development of clinical Alzheimer's, it's my experience that at-risk children can significantly reduce their chances of getting the disease by embracing healthier lifestyles and practices. Ideally, women and men should have neurocognitive baselines established at age 50, just as we have baseline bone densities and colonoscopies. This allows for the creation of simple yet tailored programs to improve cognitive health and stave off decline. In addition, there is a baseline for performance comparison down the road, should any cognitive concerns arise. Many neuropsychologists offer such testing in an outpatient setting. The tests can be time-consuming and expensive, and insurance companies may sometimes not reimburse the costs for them, but I believe the long-term benefits are significant.

Although the genetics of Alzheimer's is complex, the good news is that the most common type of Alzheimer's—the late-onset version—is the one most amenable to prevention by the adoption of effective strategies. I advocate a practical approach to prevention for children of patients but also for those of us without a family history of Alzheimer's. In one way or another, Alzheimer's disease will very likely affect either us or someone dear to us at some point in our lives.