

ALZHEIMER'S UNDER ATTACK

Armed with big data, researchers turn to customized lifestyle changes to fight the disease. BY LINDA MARSA

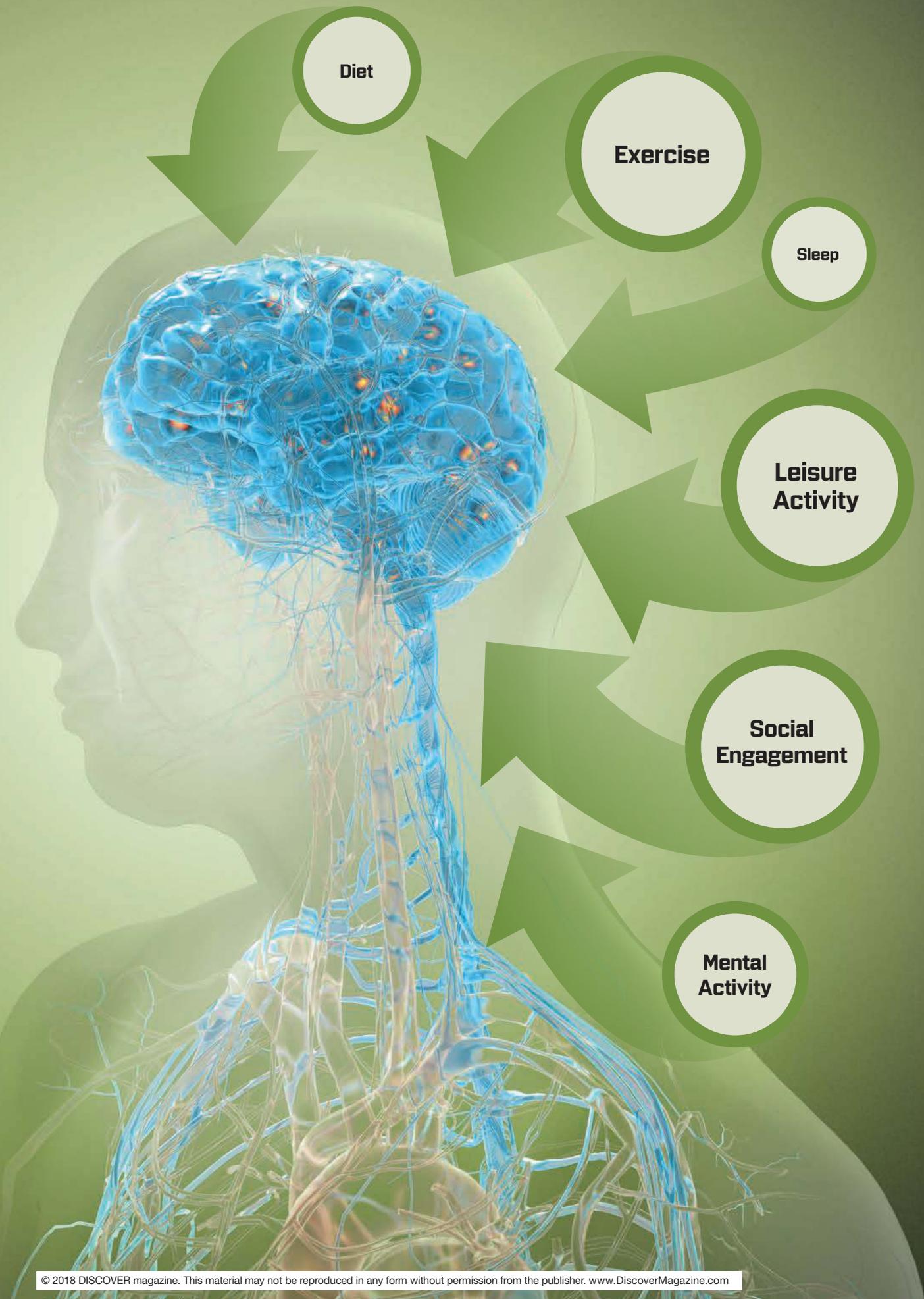
Sally Weinrich knew something was terribly wrong. On two separate occasions, she forgot to pick up her grandkids from school, and she kept mixing up their names. The 70-year-old retired nursing professor had to face reality. Her worsening symptoms — the forgetfulness and confusion, the difficulties communicating and organizing activities — weren't just stress or the normal wear and tear of aging. She lived in a matchless setting, on a lake in South Carolina, nestled in a bucolic wood. She swam daily and kayaked three days a week. But even her purposefully

healthy lifestyle couldn't protect her from the darkness she feared most: Alzheimer's disease.

In 2015, imaging tests revealed the presence of amyloid plaques, the sticky proteins associated with Alzheimer's disease that collect around brain cells and interfere with relaying messages. Weinrich also eventually learned she carried the ApoE4 gene, which increases the odds of developing Alzheimer's. The disease was diagnosed after a neuropsychological evaluation. "I felt a total sense of hopelessness," recalls Weinrich, who sank into a deep depression. "I wanted to die."

Shortly after, her husband heard a

ILLUSTRATION: BRYAN CHRISTIE DESIGN



radio program about a new treatment regimen devised by physician Dale Bredesen that seemed to reverse early stage Alzheimer's. The couple contacted the UCLA professor of neurology. Bredesen told them that, based on nearly 30 years of research, he believes Alzheimer's is triggered by a broad range of factors that upset the

exercise and restorative sleep, toxins from molds, and fat-laden fast foods. Even too much sugar, or being pre-diabetic, heightens risk. "If you look at studies, you see the signature of insulin resistance in virtually everyone with Alzheimer's," he says. "If you look at all the risk factors, so many of them are associated with the way we live."

In spring 2016, Weinrich underwent an extensive evaluation that included blood and genetic tests, online cognitive assessments and, a year later, an MRI to spot the underlying mechanisms contributing to her cognitive troubles. The imaging scan showed that her hippocampus, the brain region that regulates memory, had severely atrophied and was in the 14th percentile for her age — 86 percent of peers were better off. Bredesen says other tests he administered revealed high concentrations of fungus and mold toxins in her system, which he interpreted as residual damage from exposure to mold that had festered in the basement of one of her previous residences. Also discovered were deficiencies in other areas that might contribute to dementia, such as high levels of fasting insulin.

Bredesen crunched all these results with a computer algorithm that calculated a complex 36-point personalized therapeutic program to counteract Weinrich's specific constellation of deficits. Initially she was overwhelmed, but she gradually incorporated the changes into her lifestyle. She now sleeps about eight hours a night, fasts 14 hours a day starting in the evening and begins her morning with a 30-minute meditation. She takes a host of supplements, has cut down on carbs and increased her vegetable consumption, and gets plenty of exercise that includes yoga, Pilates, swimming, kayaking and hiking trips.

"I felt better almost immediately," says Weinrich, who once again engages in meaningful conversations and plays with her grandkids without embarrassing cognitive lapses. "I have my life back."

Weinrich's apparent improvement begs the question: Could one of our most dreaded diseases really be eased by strict adherence to almost monastically healthy habits? This new approach is based on the premise that our modern lifestyles — along with environmental assaults from infectious pathogens and toxins — are as much to blame for Alzheimer's as renegade genes or plaques.

Growing evidence suggests we may finally be on the right track.



"If you look at all the risk factors, so many of them are associated with the way we live."

—Dale Bredesen, *UCLA professor of neurology*

body's natural process of cell turnover and renewal; he didn't think it emerged from just a handful of rogue genes or plaques spreading across the brain.

Bredesen has identified more than three dozen mechanisms that amplify the biological processes that drive the disease. While these contributors by themselves aren't enough to tip the brain into a downward spiral, taken together they have a cumulative effect, resulting in the destruction of neurons and crucial signaling connections between brain cells. "Normally, synapse-forming and synapse-destroying activities are in dynamic equilibrium," explains Bredesen, but these factors can disturb this delicate balance.

These bad actors include chronic stress, a lack of



Sally Weinrich kayaks on South Carolina's Lake Murray near Columbia, something she does regularly as part of her strategy to slow the onset of Alzheimer's.

LEFT: LEEGHA HODNET; OPPOSITE: ERNIE MASTROIANNI/DISCOVER

A NEW APPROACH

Until now, the quest for effective Alzheimer's treatments has been marked by costly and high-profile failures. A stunning 99 percent of drugs tested have flopped. Nearly all the drug candidates have targeted



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—James Galvin, *neurologist and founding director of the Comprehensive Center for Brain Health at Florida Atlantic University*

one of the key hallmarks of Alzheimer's: amyloid plaques, the barnacle-like proteins long considered the main culprits behind the disease. When scientists made the link between amyloid and Alzheimer's in the 1980s, drugmakers jumped on the bandwagon in the hope of inventing a trillion-dollar drug for a progressive and fatal disease that affects more than 5 million Americans.

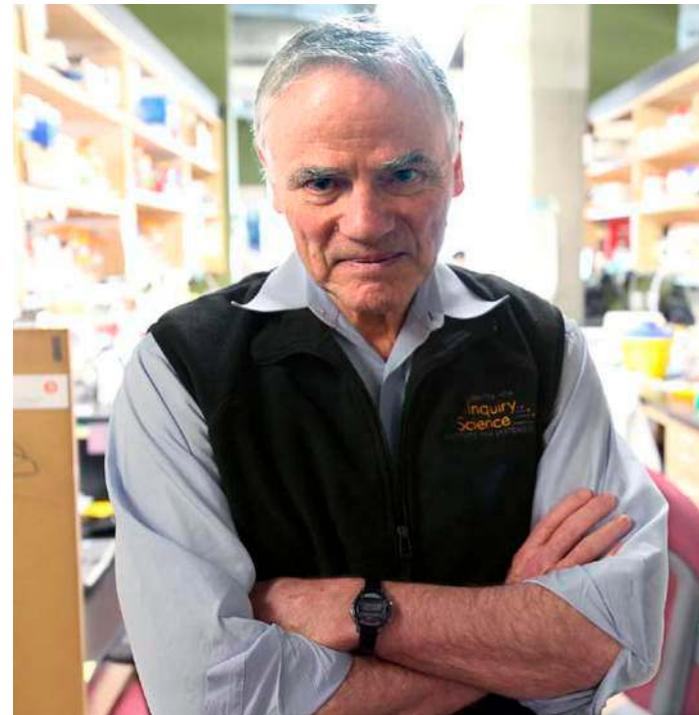
But a growing cadre of physician scientists at major research institutions, like the University of Alabama and Weill Cornell Medical Center, believe we've placed too much emphasis on these sticky proteins and have ignored other equally important miscreants. “We were barking up the wrong tree,” says David Geldmacher, founder and program director of the Alzheimer's Risk Assessment and Intervention Clinic at the University of Alabama at Birmingham.

A number of observational studies, which track people over time, have yielded insights into many of the culprits linked to Alzheimer's. The laundry list includes chronic stress, lack of exercise and restorative sleep, insulin resistance and diabetes, low kidney function, high blood pressure, inflammation from exposure to infections and environmental toxins, poor nutrition, small strokes, heart disease, concussions, genetics, and a lack of social connection and mental stimulation.

Taken together, these factors account for up to half of the risks for the disease, according to a 2011 review in *Lancet Neurology*. When people have a specific combination of these drivers, which interact differently from one person to the next, the signs and symptoms of the disease emerge. Because there seem to be multiple pathways to developing Alzheimer's, there may also be multiple ways to slow or even thwart the progress of the illness, says James Galvin, a neurologist and founding director of the Comprehensive Center for Brain Health at Florida Atlantic University in Boca Raton.

“This is where big data can come in,” Galvin says. “You can look at patterns, and when you have a cluster of patterns, you can tailor therapies based on an individual's profile. Outside of age and family history, these are risk factors that we could actually do something about and design interventions on a personalized basis. Address brain health using lifestyle modification and medication, and treat any underlying diseases, like diabetes or heart disease. And that's what we're doing — using a precision medicine-like approach that looks at each individual's risk factors and creating a treatment plan to slow or prevent the onset of disease.”

This relatively fresh perspective on Alzheimer's — both in terms of its causes and in the use of computer algorithms to devise individualized therapeutic plans — represents a dramatic shift in the way we approach the disease. Scientists like Leroy Hood, a biotech pioneer who was at the forefront of technologies behind the Human Genome Project and big data analytics, thinks this is at the leading edge of 21st-century medicine. It



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—Leroy Hood, *biotech pioneer*

hinges on using large data sets to personalize treatments and ferret out therapies that target a patient's unique genetic makeup.

Alzheimer's “is a really complex disease that has been utterly intractable,” says Hood, co-founder of the Institute for Systems Biology in Seattle and chief science officer for Providence St. Joseph Health, one of the nation's largest nonprofit health care systems. Taking a systems approach, he says, “reflects my own conviction that these complex diseases almost never respond to a single drug.”

In the meantime, though, thorny questions remain. While increasing numbers of physicians think lifestyle changes can slow or even stop the descent into

On the Wrong Track All Along?

There have been hints that amyloids weren't the toxic bad boys solely responsible for the destruction of vital brain circuits. Those clues were largely ignored. Autopsies have revealed that many people's brains are peppered with these plaques, yet their mental faculties were undiminished before they died.

For more than a decade, research suggested other factors were at play. As far back as 2005, Suzanne de la Monte, a pathologist at Brown University, had concluded that Alzheimer's was actually a form of diabetes — what she calls Type 3 diabetes. It affects the brain and has many molecular and biochemical features in common with Type 2 diabetes, which we know is a major risk factor for Alzheimer's. In one experiment, she and her colleagues blocked insulin to rats' brains. Their neurons deteriorated, they became disoriented, and their brains showed the telltale signature of Alzheimer's.

While there's a vast difference between lab animals and humans, other studies have shown that people with Type 2 diabetes are nearly twice as likely to be diagnosed with Alzheimer's, and even elevated levels of insulin significantly increased the odds that someone will develop the disorder. A pair of even more recent studies, in 2017 and 2018, have associated high blood sugar and failure to properly metabolize glucose — the fuel that revs our cells' engines — with intensifying mental foginess.

A raft of other research demonstrates that breaking a sweat works better than any medication in preserving thinking skills. That means spending an average of 45 minutes four times a week at a moderate level of intensity — the equivalent of a very brisk walk. One pilot study of 65 volunteers with mild cognitive impairment and pre-diabetes looked at the effects of six months of regular high-intensity aerobic exercise. Results showed exercise enhanced executive function — the ability to plan and organize — and increased blood flow to regions vulnerable to Alzheimer's. “They even had a reduction in tau tangles,” which are another hallmark of Alzheimer's, says Laura Baker, a cognitive neuroscientist at the Wake Forest School of Medicine in Winston-Salem, North Carolina, who led the study. “No drug can do that.”

This research has been expanded into a larger trial, called EXERT, which will eventually include 300 people between the ages of 65 and 89 who have mild cognitive impairment. “We're really hoping to push the envelope on whether we can improve memory with exercise,” says Baker, who also is associate director of the Wake Forest Alzheimer's Disease Core Center.

What's more, a series of other studies, including a major 2017 review by *The Lancet*, have identified a clutch of modifiable risk factors for Alzheimer's: depression, obesity, physical inactivity, smoking, hearing loss, high blood pressure, diabetes and a lack of education. The review concluded that improving on these risk factors could prevent more than a third of dementia cases across the globe.

The Alzheimer's Association has launched the POINTER study, a more than \$20 million two-year test that will examine whether lifestyle interventions can prevent dementia in 2,000 older adults. This research is modeled on a 2015 Finnish study of more than 1,200 elderly at risk for cognitive decline. That study found that mental acuity could be preserved with a regimen of physical activity, proper diet, mental exercises, social engagement and intensive monitoring of vascular and metabolic risk factors. “In the best-case scenario, if we could keep the disease from worsening so their progression is slowed,” says Baker, a co-principal investigator on this study, “I'd count that as a success.” —L.M.

Alzheimer's, in the absence of definitive clinical trials involving hundreds of people — the gold standard to prove efficacy — some scientists are deeply skeptical.

“A variety of factors are linked to Alzheimer's, but association doesn't prove causation,” says Victor Henderson, the director of Stanford University's Alzheimer's Disease Research Center. “Alzheimer's is very complex, and one simplistic approach isn't likely to be the magic bullet. If there were simple answers, people would have come up with them already.”

SENDING A SIGNAL

Treating Alzheimer's has been a challenge because, until now, little meaningful progress has been made. Neurologists on the front lines have felt powerless, watching their patients disappear into the sinkhole of forgetfulness.

Big Pharma's focus on a one-size-fits-all anti-amyloid drug, and the billions in funding that went with it, largely eclipsed a dramatically different story that was quietly emerging from independent academic studies over the past decade: Other health conditions, such as our sedentary lifestyles, poor eating habits, Type 2 diabetes, insulin resistance and skyrocketing obesity, play a huge role. “But you can't package or patent a lifestyle,” Galvin dryly observes.

In his darkest moments, Galvin wondered if he was doing anything for anybody. He had so few weapons in his treatment arsenal — only a handful of marginally beneficial drugs approved decades

ago that can temporarily enhance thinking and functioning. Studies that linked Alzheimer's to a range of modifiable lifestyle factors prompted him to make subtle changes in his practice, and he began to more aggressively treat the health conditions that contribute to the disease. He'd prescribe medication to lower his patients' blood pressure, statins to control cholesterol, or suggest exercise regimens or dietary changes to lessen insulin resistance and improve brain health. “I started to see that my patients seemed to progress much slower than my colleagues', and the families would tell me the same things,” Galvin recalls. He discovered some of his fellow neurologists were taking a similar tack: “The same lightbulb is going off.”

At the University of Alabama at Birmingham, Geldmacher gives each patient a detailed and personalized risk assessment that encompasses family history, performance on tests of mental acuity and results of MRI scans. “By controlling their risks, people can maintain their well-being through physical exercise, mental stimulation and a healthy diet,” says Geldmacher. “Those three things may help lower their risk for the disease or slow it down. That's where the field is going.”

Richard Isaacson, the founder and director of the Alzheimer's Prevention Clinic at New York Presbyterian Weill Cornell Medical Center, spends hours with each patient doing a thorough health analysis. He uses cognitive tests, body measurements



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—Richard Isaacson, founder and director of the Alzheimer's Prevention Clinic at Weill Cornell Medical Center

and brain health computer assessments, as well as lab tests and imaging exams (MRI or PET scans) to pinpoint areas that can increase the odds of developing Alzheimer's. “We look at genetics, we look at cholesterol, we look at glucose metabolism, we look at body fat,” says Isaacson, who was inspired to do this work after watching four family members succumb to the disease. “Then we triangulate this information, using each data point with the context of one another.”

Based on their risk factors, patients are prescribed a regimen of exercise, methods to reduce stress and get more restorative sleep, prescription and over-the-counter medications, and even nutritional supplements to compensate for their deficits. In people who dutifully follow the program, Isaacson says early research indicates

Diagnosing Alzheimer's Can Be Difficult

It is tricky to diagnose Alzheimer's disease because it shares symptoms with many other complications of aging, such as stroke, tumors, sleep disturbances, Parkinson's disease and other forms of dementia. Even side effects from certain medications can mimic the signs of the disease.

Until now, diagnosis was based on observation of the constellation of symptoms associated with the mind-robbing disorder, such as forgetfulness, fuzzy thinking, confusion, difficulty concentrating, or changes in behavior, personality, and the ability to function normally. In addition, extensive neuropsychological evaluations look at such factors as how quickly people can process information, solve problems or remember words. Other standard medical tests, such as blood and urine tests, can spot other potential causes of the problem. Thanks to advances in a type of brain imaging technique called a PET scan, scientists are able, in a research setting, to identify what researchers believe is one of Alzheimer's biological markers: amyloid plaques. Another PET scan innovation, currently under development, may be able to detect the abnormal protein tau, thought to be another telltale sign of Alzheimer's.

But even with better testing, a conclusive diagnosis can remain elusive. Researchers are finding that Alzheimer's symptoms and the presence of amyloid and tau do not necessarily go hand in hand.

In 2011, a researcher did a postmortem analysis of 426 Japanese-American residents of Hawaii, about half of whom had been diagnosed with some form of dementia, typically Alzheimer's. According to the autopsies, roughly half of that group had been misdiagnosed as having Alzheimer's — their brains didn't show evidence of the brain lesions typical of the disease. At a 2016 conference, Canadian scientists presented preliminary findings, based on more than 1,000 individuals, that patients were correctly diagnosed only 78 percent of the time. In nearly 11 percent of cases, patients thought to have Alzheimer's actually didn't, while another 11 percent did have the disease but weren't diagnosed.

Scientists are now investigating a number of disease markers, such as genes or disease-related debris or abnormal proteins in the spinal fluid or blood, that may more reliably and accurately diagnose Alzheimer's. —L.M.

The Bredesen Protocol

Dale Bredesen's protocol is designed as a comprehensive personalized program that aims to reverse the biological causes of cognitive decline and early Alzheimer's disease. Bredesen believes that Alzheimer's isn't just one disease but that there are three distinct subtypes driven by different biological processes, and each distinct condition requires a customized treatment regimen.

Type 1 of the disease is associated with systemic inflammation. Inflammation is not present in Type 2, but abnormal metabolic markers are, including insulin resistance and extremely low levels of certain vitamins and hormones. Type 3 is characterized by a specific type of brain atrophy, seen on an MRI, and generally strikes younger individuals with no family history of Alzheimer's. This subtype may be associated with chronic exposure to

environmental toxins, such as certain metals and mold, but the research is currently inconclusive.

The first step is to undergo what Bredesen calls a “cognoscopy,” which is a combination of blood tests, genetic evaluations, cognitive assessments and an MRI, which measures brain volumes to identify areas of shrinkage. The evaluation is designed to pinpoint the underlying mechanisms that Bredesen believes are the root causes behind cognitive decline.

The results are then crunched using a computer algorithm to customize a plan based on each person's particular deficiencies and genetic makeup.

Typically, each plan encompasses several key elements to reverse inflammation, insulin resistance and destruction of vital brain structures. They include:

→ Optimizing sleep and getting at least eight hours of shut-eye every night.

→ Fasting at least 12 hours a day; patients usually don't eat anything after 7 p.m. until the next morning.

→ Frequent yoga and meditation sessions to relieve stress.

→ Aerobic exercise for 30 to 60 minutes, at least five times a week.

→ Brain training exercises for 30 minutes, three times a week.

→ Eating a mostly plant-based diet: broccoli, cauliflower, Brussels sprouts, leafy green vegetables (kale, spinach, lettuce).

→ Cutting out high-mercury fish: tuna, shark and swordfish.

→ Drinking plenty of water.

→ Eliminating gluten and sugars. Cutting out simple carbs (bread, pasta, rice, cookies, cakes, candy, sodas). —L.M.

how best to test a treatment platform that can be used everywhere. “We’re trying to lay the groundwork for Alzheimer’s prevention and figure out what tools we should be using and what works best,” says Isaacson. “But the field is still in its infancy, so we literally learn every day.”

BARNSTORMING FOR A FIX

In the meantime, Bredesen, the UCLA neurology professor, has been touring around the country, promoting his program through his best-selling book, *The End of Alzheimer’s*, and giving lectures at scientific conferences and talks to community groups. Still, his controversial approach has more than its share of detractors. “You don’t want vulnerable people spending money on something that isn’t yet proven to work or be safe,” says Keith Fargo, director of scientific programs for the Alzheimer’s Association.

But many people who followed his program seem to benefit. While their stories are anecdotal and the details differ, there are some common threads, with several talking about reclaiming pieces of themselves they thought had vanished forever. (They have requested anonymity because of the stigma of Alzheimer’s

The story of one successful entrepreneur is especially significant because his decline was well documented. He had gotten PET scans and neuropsychological tests every few years, starting in 2003. The imaging tests revealed patterns of early stage Alzheimer’s, and subsequently, he learned he carried the gene variant. As the years went by, friends and colleagues noticed his deterioration. By 2013, tests indicated his decline had accelerated, and his neuropsychologist suggested he shutter his businesses. “It was very sobering,” he says. “I thought about selling my business while there was still something to sell.”

The businessman met with Bredesen, who used the data culled from his evaluations and crunched the information in a software algorithm to devise a personal plan that the entrepreneur dutifully followed. Two years later, another battery of neuropsychological tests revealed his scores had improved. His verbal learning and memory and auditory memory had jumped from substandard to superior. His neuropsychologist had never seen anyone make this kind of recovery in his 30-year career. “You can’t fake these,” the entrepreneur says now. “It’s not like you can drink a cup of coffee and do really well.”

While the evidence remains largely preliminary, these individual cases have reached a critical mass, which indicates something is happening that needs to be explored in a more rigorous way.

disease.) One middle-aged nonprofit director living near Chicago noticed she was becoming forgetful and was horrified to learn that she carried two copies of the ApoE4 gene variant, meaning she has an especially high chance of developing Alzheimer’s. Now 56, her symptoms have subsided after a stringent program of diet, exercise and an array of supplements.

A lawyer on the East Coast was only 40 when she could sense she was being pulled into the quicksand of Alzheimer’s. Her father was already gripped by the disease, and it had claimed her grandmother, too. Within a decade, her thinking became muddled, and she was at a loss for words and language — she’d forgotten Chinese and Russian. After six months following Bredesen’s protocol, the fog lifted, and within two years, she could speak foreign languages proficiently again.

These approaches offer hope to the millions at risk for Alzheimer’s and their families. In the near future, these physicians believe Alzheimer’s could become a chronic but manageable disease, much like diabetes or heart disease. Like these life-threatening ills, if Alzheimer’s is left unchecked, it can be severely debilitating and deadly. But proper treatment and lifestyle changes may be able to stave off symptoms for years, enabling people to live more satisfying, productive lives.

“Alzheimer’s is a life course disease, meaning that cognitive health starts in the womb and is influenced by what we do throughout our lives,” says Isaacson. “By treating the underlying conditions, we can have a positive effect on brain health, reduce risk and even prevent the disease.” ■

Linda Marsa is a Discover contributing editor.

DAN BISHOP/DISCOVER

ALZHEIMER’S DISEASE A Steady Uptick

5.7 MILLION
Americans are living
with Alzheimer’s

By 2050, this number
is projected to rise
to nearly
14 MILLION

ALZHEIMER’S
DISEASE is the
6th
leading cause of
death in the
United States

Every
**65
SECONDS**
someone in the U.S.
develops Alzheimer’s
disease

Between
2000 and
2015, deaths
from heart
disease
have
decreased
11%

Deaths from
Alzheimer’s
disease
have
increased
123%

In 2018, Alzheimer’s
and other dementias
will cost the nation
\$277 BILLION

By 2050, these costs
could rise as high as
\$1.1 TRILLION

Cost of care by payment source

- Medicare \$140 billion, 50%
- Medicaid \$47B, 17%
- Out of pocket \$60B, 22%
- Other \$30B, 11%

Age of people with Alzheimer’s in the U.S., 2018

- 85+ years, 37%
- 75-84 years, 44%
- 65-74 years, 16%
- <65 years, 4%

Total greater than 100 percent
due to rounding

SOURCE: Alzheimer’s Association