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THE NEW AGE OF ALZHEIMER'S

*The soaring burden of dementia threatens global health.
Science is paving new paths to solutions.*

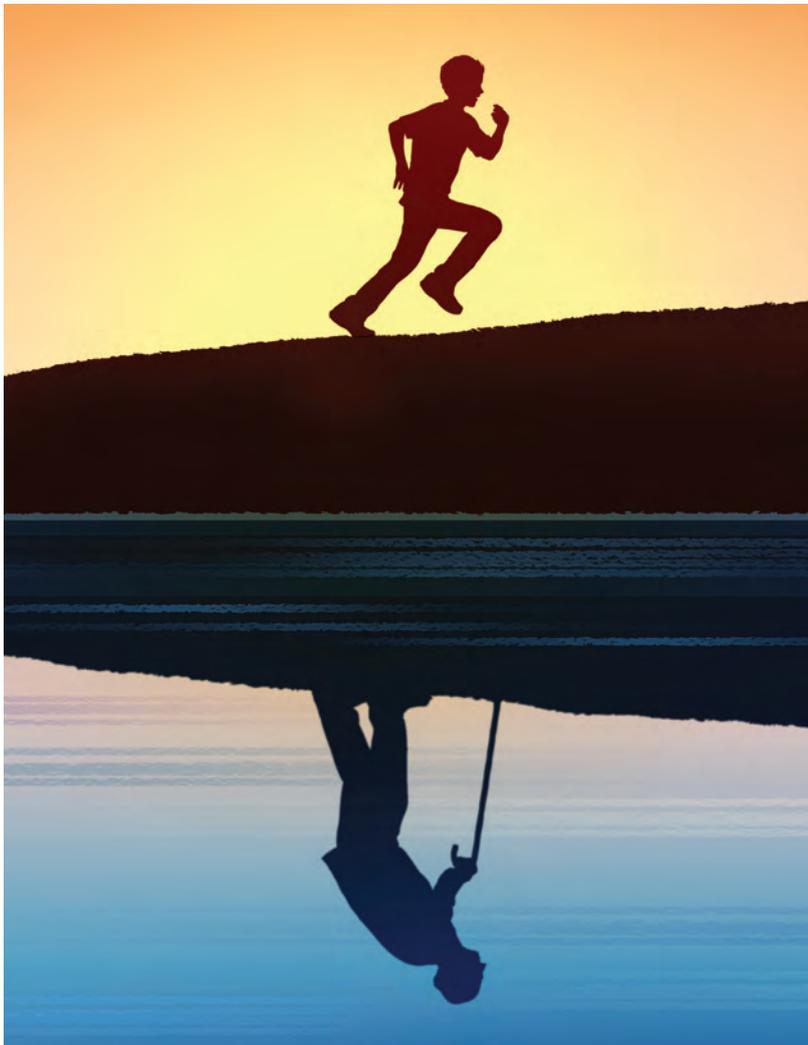
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“It’s a very sad condition... science, hopefully, will one day cure it.”

A Crazy Little Thing Called Hope

BY JEREMY ABBATE

The hospice nurse who, in the final days of my father’s care, was one of our family’s rocks of stability, put two fingers gently to his neck as a last read of his vital signs. “Yes,” she said, reassuringly and tenderly, as she looked at me and my mother, “he’s gone.”

It was a humid afternoon in August 2017. We were gathered in the family room of the New Jersey home in which I had grown up, leaning over a medical bed set up for my father in the final six weeks of his life.

While a day of haunting sorrow, we had cause to be grateful: my father, diagnosed with frontotemporal dementia (FTD) earlier that spring, which had developed into full-blown ALS, went quickly. His earliest perceptible symptoms appeared in February of that year, and he took his last breath in August. He avoided the fate of his two older sisters, his mother, and his father, each of whom suffered a long, protracted, heart-breaking decline from Alzheimer’s disease.

I was 11 years old when I first meaningfully heard of Alzheimer’s. En route to a visit with my grandparents, my mother warned me not to be surprised if my grandfather didn’t recognize me or remember my name. “It’s a very sad condition,” she explained, but added that “science, hopefully, will one day cure it.”

That’s how the trajectory of devastation from Alzheimer’s began on my father’s side of the family, as it has for millions like us across the country and the world: all of us seeking that elusive human comforter, hope.

In the 1980s, as the nascent era of modern biotechnology began offering better tools for conditions such as diabetes and cancer (and, soon after, HIV and many other diseases), research into Alzheimer's started to ramp up in earnest. The human neurological system is by nature difficult to study, and clarifying the precise pathogenesis and modulation of a disease as complex as Alzheimer's presented a Herculean challenge for researchers and allied healthcare communities across the world at the time.

Back then, patients and families had little in the way of hope. We were told to maybe avoid certain substances like aluminum in deodorants. Early genetic tests could offer some insight into gene variants that might imply more likelihood of the disease. Memory-enhancing drugs called cholinesterase inhibitors that came on the scene in the 1990s were minimally effective—they were, as my physician friends confessed, prescribed more for the benefit of the family than the patient.

Real progress seemed far off. At the time, Alzheimer's was always diagnosed well after symptoms appeared, and the emotional, financial, and logistical burdens on patients and families made the diagnosis a moment of dread. With decline and heartache on the horizon, facing Alzheimer's then was like holding the ocean back with a broom.

While the arc of scientific research is long, it did eventually bend towards progress. At the beginning of the current decade, while the world was in the throes of another urgent health crisis, a global viral pandemic, those of us tracking milestones in Alzheimer's began to realize we were in a much different place than we had been a few years earlier. For the

first time, real hope, real progress, had appeared on the horizon.

Progress came in stages and had a powerful cumulative effect. Clinical data that had been percolating for years were revealing an ever-sharper picture of how lifestyle and nutrition choices can alter one's susceptibility to Alzheimer's. A much more effective diagnostic arsenal and better tools for measuring neural activ-

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ity were generating penetrating insights into brain biology and brain health.

Meanwhile, the field achieved an incredibly important milestone: the first disease-modifying therapies for Alzheimer's. While they're not a cure and they have potential side effects, these therapies are no small feat: They may have a significant effect on slowing disease progression for those in Alzheimer's early stages. This is cause for celebration after several frustrating decades of nothing.

In the context of other recent scientific and social advances—real progress in gene therapy and gene editing; a post-pandemic ethos of collaboration among researchers across borders; a pro-

found awareness of how governments can catalyze and de-risk much-needed innovation during a crisis—the landscape for Alzheimer's is no longer bleak. More early diagnosis and even more attention on phenomic factors (the sum total of our genetic, environmental and behavioral inputs) will no doubt keep up the momentum. There is a long journey ahead, to be sure. But there is also a palpable sense, for those deeply embedded in the community and the public in general, that hope is at hand.

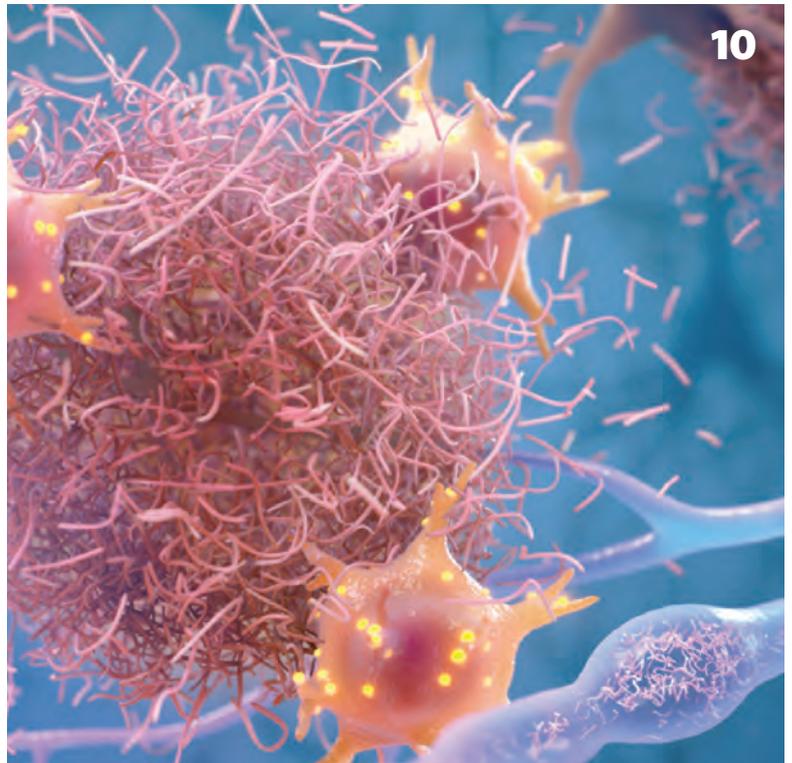
As someone ensconced in the world of science media and who attends several annual conferences, I happily come across champions of healthcare frequently. It was at one such conference that I met Phyllis Barkman Ferrell, an advisor to this special edition and media project from Scientific American Custom Media, and a kindred spirit in the fight against Alzheimer's who has also personally been affected by the disease. Phyllis introduced me to the team at the Davos Alzheimer's Collaborative (DAC), a partner in this media effort and an organization emblematic of the global scale to which we need to direct our efforts, including its dynamic chairman, George Vradenburg, with whom I had an instant connection because of our shared passion for this topic.

This special edition and DAC partnership are dedicated to all our families, and to the many families and patients worldwide seeking progress on this horrible disease. It is an exploration and celebration of what we can achieve if we work together. And it is, above all, a celebration of what I've been chasing since I was 11 years old: a new era of hope.

Jeremy Abbate is the publisher of Scientific American.

[CONTENTS]

on the cover:
illustration by
Harol Bustos



8 Seize This Global Moment

Defeating Alzheimer's is now possible, if we meet the global health challenge the disease has created.

BY GEORGE VRADENBURG
AND OLIVIER SCHWAB

10 A Seismic Shift in Alzheimer's

Recent advances in early detection and treatment have galvanized scientists and given hope to patients.

BY DAVID H. FREEDMAN



17 Stopping Alzheimer's Ahead of Symptoms

Can drugs given early stave off cognitive decline?

BY DAVID H. FREEDMAN

21 "You should know, I'm not a saint."

Most caregivers of people with Alzheimer's find themselves behaving in counterproductive ways. The disease affects their brains, too.

BY DASHA KIPER

24 The Ten Trillion Dollar Disease

A new model of Alzheimer's predicts a staggering economic burden and justifies major investments in research, testing, treatments and public-health outreach.

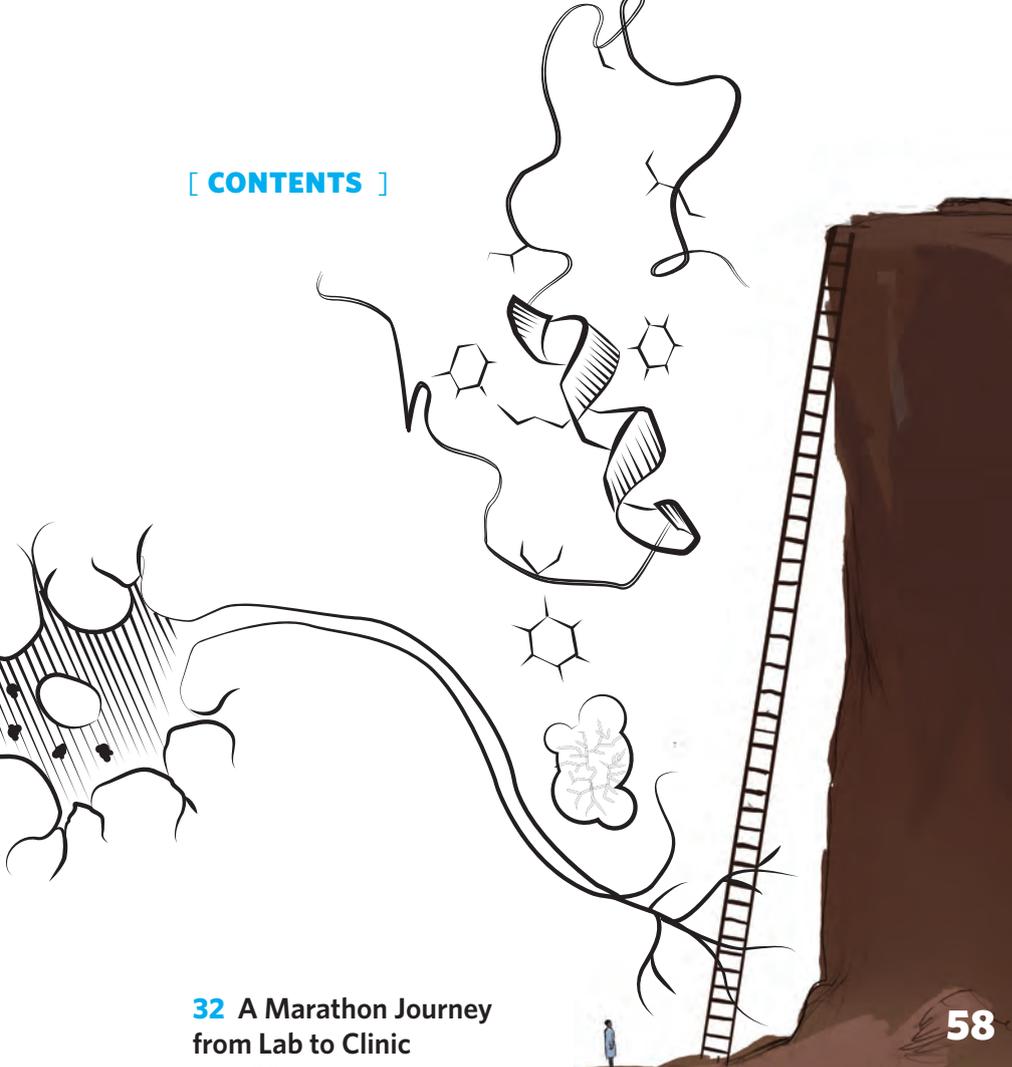
BY DAVID BLOOM, SIMIAO CHEN
AND ARINDAM NANDI

INFOGRAPHIC

28 The Ballooning Economic Impact of Dementia

A new model predicts Alzheimer's and other dementias will cost \$17 trillion a year by 2050.

[CONTENTS]



32 A Marathon Journey from Lab to Clinic

How 20 years of molecular detective work led to the first effective Alzheimer's drugs.
BY ESTHER LANDHUIS

INFOGRAPHIC

36 Alzheimer's Impact on the Brain

The latest neuroscience tracks where the disease begins and how it progresses.

42 An Alzheimer's Test for Everyone

Annual checkups may soon include a blood test that screens people for Alzheimer's, ushering in a new era of treatments.
BY SUZANNE SCHINDLER

INFOGRAPHIC

47 How to Detect Alzheimer's Before Symptoms Appear

New technologies that catch the earliest signs of dementia will be critical for slowing, and one day stopping, disease progression.

48 Beyond Pen and Paper

Digital cognitive tests designed to spot early signs of Alzheimer's are beginning to hit the market.
BY ADAM PIORE

INFOGRAPHIC

51 Gateway to the Brain

The eyes are windows to the central nervous system and may offer new, noninvasive screening methods.

INFOGRAPHIC

52 Risk Factors for Alzheimer's

Genes and age play a big role in susceptibility to the disease, but choices make a difference, too.

54 A Grassroots Approach to Diversity

Community engagement is a must for ensuring clinical trial diversity and effective treatments for all.
BY SIMAR BAJAJ

42



Q&A

58 "We need genomics at a global scale"

Research on diverse populations is essential to beat a disease as complex as Alzheimer's, says Elias Zerhouni.
BY FRED GUTERL

64 The Urgent Challenge of Scale

To bring new tests and treatments to the people who need them, healthcare systems must transform how they approach dementia care.
BY HILARY EVANS AND JOHN BELL

INFOGRAPHIC

68 The Approaching Alzheimer's Wave

Dementia is on the rise in every region of the world, with vast implications for public health.



LESSONS FROM AROUND THE GLOBE

Community-based programs are exploring new ways of managing Alzheimer's care.

70 A Gentle Sleight of Hand

The village of Volta Redonda in Brazil has built a model day-care center for Alzheimer's patients.

BY MAC MARGOLIS

72 Preaching Brain Health to Young and Old Alike

Scotland is putting in place an infrastructure for preventing Alzheimer's.

BY WILLIAM UNDERHILL

74 It Takes a Village

Community leaders in Kenya are leading the charge to increase Alzheimer's awareness and reduce stigma.

BY APRIL REESE

76 Teaching Good Brain Hygiene

In Japan, where more than 90,000 people are 100 years or older, clinicians are advocating lifestyle habits that reduce the risk of Alzheimer's.

BY MIHOKO IIDA

78 Taking It to the Streets

In Armenia, clinicians travel the countryside in a minivan, conducting tests for Alzheimer's.

BY APRIL REESE

Q&A

80 "We're at a tipping point with Alzheimer's"

Bill Gates talks about his own experience as a caregiver and what needs to be done to fight this disease.

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Seize This Global Moment

Defeating Alzheimer's is now possible, if we meet the global health challenge the disease has created.

BY GEORGE VRADENBURG
AND OLIVIER SCHWAB

On behalf of the 55 million people worldwide who live with Alzheimer's disease, the millions more who shoulder the burden of care and loss, and the younger generations whose futures are clouded by the threat of this disease, we issue a call to action.

The time is ripe. For the first time, we have an opportunity to defeat this disease, which robs so many otherwise healthy people of their memories and their identities and causes so much suffering and loss to them, their loved ones and society at large.

In recent years, scientists have made startling advances in their ability to detect Alzheimer's disease in the early stages, when treatments are most effective. Drugs are now available that can slow the progress of the disease, having gone from the lab to pharmacy shelves, and more are in the pipeline.

The arrival of these twin advances in testing and treatments has galvanized medical researchers, entrepreneurs and healthcare professionals. Several big pharmaceutical firms that had backed away from the disease, because it was so complex that it defied quick solutions, are once again making big investments. Biotech firms are working to commercialize new technologies, such as blood biomarker tests and cognitive tests that can help in diagnostics and screening. What's more, regulators have shown a new willingness to move drugs quickly through the approval process, which is spurring innovation.

This good news brings a new challenge: getting these tests and treatments to the millions of people in all corners of the world who need them. We formed the Davos Alzheimer's Collaborative (DAC) in part to address this challenge.

Part of this task involves bolstering our ability to detect Alzheimer's early in the disease. Several blood tests that are currently on the market can measure tel-

take?" Doctors will need to figure out how to build Alzheimer's testing into their routine clinical practice. DAC is helping them do exactly that.

Rectifying inequities is critical. So far, researchers developing treatments and tests have focused on people of northern European descent, neglecting the rest of the world, where the vast majority of Alzheimer's patients are to be

Europe, China, India and other nations need to join the U.S., U.K. and others in the fight against this disease.

The World Economic Forum and the Global CEO Initiative on Alzheimer's Disease came together to form DAC, because we need an international organization that can coordinate an approach to Alzheimer's disease that resembles the global effort to fight infectious disease. DAC was modeled on organizations such as Gavi, the Vaccine Alliance; The Coalition for Epidemic Preparedness Innovations and The Global Fund, which were formed as mechanisms for battling malaria, polio, influenza and other infectious diseases around the world.

Defeating Alzheimer's will require a massive cooperative effort. DAC is already working to speed innovation and prepare health-care systems to implement new technologies and strategies. We are enlisting corporate executives, government leaders and nongovernmental organizations in an effort to ease the burden of this disease and end the suffering it causes.

In the following pages you will read about our efforts thus far to make health systems better able to detect the disease early, reach underserved populations and to find new, innovative ways of bringing more providers to the frontlines.

Leveraging what we are learning from around the world, we are calling on governments to increase their investments in research, healthcare and treatments. Working together, we can beat this disease rapidly and comprehensively.

George Vradenburg is the founding chairman of the Davos Alzheimer's Collaborative. Olivier Schwab is the managing director of the World Economic Forum.



“We are calling on governments worldwide to increase their investments in research, healthcare and treatments.”

lale proteins, and more are due in the coming months. We need to make these tests cost-effective and plentiful.

Even though much of the technology needed for early detection is already in place, policymakers are underestimating the resources and assistance that clinics, doctors' offices and public-health officials will require to adopt and implement early detection.

Putting tools in the hands of consumers is another effective strategy that could be helpful in early detection. Digital assessment tools are now available that allow you to test yourself for cognitive impairment—whether it's memory, judgment or orientation. Such tests can help manage the screening workload in clinics.

We also need to raise public awareness about the new outlook for Alzheimer's, so that people know there's something they can do about the disease other than fear it. People should be asking their doctors, “How is my brain health? Is there a blood test I can

found. This is unfair, and it is also bad science, because it leaves out information contained in the full panoply of human genetic diversity. Research organizations are making efforts to rectify this gap, but much remains to be done.

Healthcare systems around the world, already strained by the growing prevalence of Alzheimer's and other diseases, will need help in handling the new protocols for screening and treatment.

To seize this global moment, we must work together. At present, the field of Alzheimer's is fragmented. Academics work with their cohorts, businesses have their product strategies, governments focus on their own citizens. This compartmentalization is a wasted opportunity to pool our knowledge and scale our resources.

Governments around the world need to step up their game. The U.S. National Institutes of Health spent about \$400 million a year on Alzheimer's disease in 2010; it now spends \$3.7 billion. No other government or region comes close.



A Seismic Shift in Alzheimer's

Recent advances in early detection and treatment have galvanized scientists and given hope to patients. BY DAVID H. FREEDMAN

ILLUSTRATIONS BY HAROL BUSTOS

Not long ago, the only way to tell whether a patient with dementia had Alzheimer's disease was to do an autopsy for the presence of amyloid plaque and other signs of degeneration in the brain. In recent years, new tests can detect the presence of amyloid, a telltale protein of Alzheimer's, and other biological signs long before the onset of symptoms. Soon, doctors may routinely make definitive diagnoses of Alzheimer's with a simple blood test, even before symptoms of dementia become apparent.

An early diagnosis of Alzheimer's is not worth much if there's nothing you can do about it. But new effective treatments that slow the progress of the disease have become available: the drug lecanemab, recently approved by the FDA, and a new one called donanemab, which slowed cognitive decline in trials. The availability of effective treatments, together with technologies for detecting Alzheimer's in the early stages, when those treatments can be most effective, have radically changed the outlook for Alzheimer's patients and their loved ones. The notion of attacking Alzheimer's in the brain before clinical symptoms emerge, long merely an aspiration, is starting to look like a practical strategy.

Advances in early detection and treatment come as welcome news, but they imply a looming public-health challenge. Being able to screen for Alzheimer's and administer treatments before symptoms arise would vastly increase the number of people who need attention. Public-health institutions are almost universally inadequate for the task. There are large disparities in the impact of Alzheimer's and in access to care in the U.S. and around the world. Pilot programs in communities around the world are showing how it might be done.

Meanwhile, the new optimism rippling through the research field is palpable. "Having been in this field for 20 years, the idea that I can finally offer treatments that biologically slow the disease is incredibly exciting," says Gil Rabinovici, who directs the Alzheimer's Disease Research Center at the University of California, San Francisco. "There's a lot more work to do, but the feeling is that our understanding and ability to measure and treat the disease is coming together in a new way."

"The feeling is that our understanding and ability to measure and treat the disease is coming together in a new way."

An enormous toll

About one in nine Americans over 65 have Alzheimer's disease, according to figures from the Alzheimer's Association. The numbers are higher for several segments of the population, including women, Black Americans and Hispanics. The number of people with Alzheimer's is expected to more than double in 25 years.

It is a cruel, relentless disease. "It progressively robs you of who you are," says neuroscientist Donna Wilcock, director of Indiana University's Center for Neurodegenerative Disorders. Families carry much of the weight, she adds. The annual cost of Alzheimer's care in the U.S. has reached \$345 billion, the Alzheimer's Association estimates—and that doesn't count the \$340 billion worth of unpaid care put in by an estimated 11 million family members and other caregivers of U.S. Alzheimer's patients in 2022. Other estimates run even higher (see "The Ten Trillion Dollar Disease," on page 24).

Modern medicine has made enormous strides in treating cancer, diabetes, heart disease, and even other neurodegenerative diseases such as Parkinson's and multiple sclerosis. But for years, everything medicine could throw at Alzheimer's seemed to bounce off. The main research strategy has been to try to come up with drugs that attack the plaque that for more than a century has been known to be present in the brain tissue of deceased Alzheimer's patients. But the dozens of experimental drugs that reduced brain plaque in mice with Alzheimer's-like symptoms failed to make any detectable difference in cognitive decline in human drug trials.

Then, in 2021, a leap of progress came with the Food and Drug Administration approval of aducanumab, an amyloid-beta-attacking monoclonal antibody—a lab-made version of an antibody found in the human immune system. Aducanumab was the first drug ever approved for slowing cognitive decline in Alzheimer's patients. But it was a controversial decision, in part because trial data showed at best hints of a possible small average slowing in cognitive decline.

Much of that uncertainty evaporated in January 2023, when the FDA approved a second plaque-fighting monoclonal antibody, lecanemab. This time, the regulators saw clear evidence that on average the

drug slowed the cognitive decline in patients with early symptoms of Alzheimer's. And that thrilling news was still reverberating through the research and patient communities when data released in July 2023 from a phase 3 trial of a third monoclonal antibody, donanemab, showed even better results, slowing the decline in memory and thinking by 35 percent compared to placebo. Almost half the study subjects who received donanemab showed no worsening of symptoms during a year of treatment, compared to only 29 percent in the placebo group.

"This is one of the things that patients and families say is important to them—to stay at the same level longer to keep doing what they enjoy doing," says Mark Mintun, who heads neuroscience research and development at Eli Lilly, the pharmaceutical company that developed donanemab.

The sudden appearance of helpful treatments has been revitalizing for both the patient and research communities, says Indiana University's Wilcock. "Patients and families had lost a lot of hope, and this restores it," she says. "I truly believe it's the beginning of the successful treatment of the disease."

Continually better drugs are likely to follow in a steady stream over the coming years and decades, experts say. Alzheimer's research may be similar to multiple sclerosis, another complex neurological disease. The first approved drugs in the 1990s were about 30 percent effective, and now several drugs are more than 80 percent effective.

Diagnostics breakthroughs

Several factors have led to the sudden emergence of effective drugs. One is that the newer drugs are aiming at the right kind of amyloid plaque. There are many types, most emerging from variations of the amyloid beta peptide, but research has gradually pointed at particular forms, giving drug developers more specific and fruitful targets. A second factor is the improving ability to produce monoclonal antibodies that are more effective at hitting their targets.

But what may be the biggest single factor in the breakthrough treatment progress isn't really about the treatments themselves. Rather, it's better diagnosis.

A positron emission tomography, or PET, scan, involves injecting a radioactive tracer compound into a patient and then scanning for photons emitted. If the tracer binds mostly to something in the body associated with a particular disease, then the scan can be useful in diagnosis. PET scans capable of detect-

ing amyloid beta plaque in living human patients have been around since 2004, but the early versions required massive machines that cost more than a million dollars to install, and even then the results didn't give a reliable diagnosis of Alzheimer's disease. It wasn't until 2017 that affordable PET scans became capable of reliable plaque-based Alzheimer's disease diagnosis.

When clinicians and researchers started accumulating results from those scans, they discovered two things. First, as many of 30 percent of people diagnosed with Alzheimer's disease based on cognitive assessments didn't have high levels of the plaque, which meant they had a different type of dementia and had been misdiagnosed. Thus, some of the plaque-reducing drugs that had failed in earlier trials probably hadn't done as well as they might have because they included patients who had a different condition that had little to do with plaque.

Second, PET scan data clearly demonstrated that people with no clinical symptoms sometimes had high levels of plaque, and those people would usually go on to develop symptoms years later. In other words, people with high levels of plaque but no signs of cognitive impairment were simply earlier in the disease progression.

Researchers had long believed that the biological seeds of Alzheimer's are planted long before—even decades before—cognitive impairment is clearly diagnosable, but they had no way of knowing which people were on that path. With PET scans closing that gap, drug trials could include patients positively diagnosed, through detection of plaque, while in the earlier stages of the disease, when a plaque-clearing drug might have a better chance of heading off damage. What's more, ongoing PET scans can quickly reveal whether a trial drug is actually reducing brain plaque, making it easier to focus on drugs that had the best chance of working. Perhaps most important, these scans can reliably identify patients who have the disease in order to know which ones will likely benefit from approved treatments.

All told, the ability to diagnose the disease more surely and earlier, and to track its biological progression, has helped revolutionize the effort to develop and prescribe treatments.

"We don't have to wait for someone to have symptoms to know if they have cancer," says UCSF's Rabinovici. "But 100 years after the initial Alzheimer's case reports, we were still diagnosing by clinical

"Alzheimer's progressively robs you of who you are."

symptoms confirmed at autopsy. These scans represent the modernization of Alzheimer's care."

Even better, blood tests are emerging that can pick up biomarkers correlated with the buildup of amyloid plaque in the brain, at much lower cost and higher convenience than a PET scan or a spinal tap, the other way of detecting signs of plaque. Blood tests could eventually become a routine screen for people who are in their 50s, when someone on track to experience cognitive decline from Alzheimer's in their 70s would probably already have detectable levels of plaque.

Better, less expensive and more convenient diagnostic tests also mean people could more easily get a shot at one of the new plaque-clearing drugs when they may be able to do the most good. Research has shown that patients with mild cognitive decline do better when treated in early stage of the disease. In presymptomatic patients—that is, those who show no cognitive decline, but test positive for plaque—it's still unproven whether treating them with anti-plaque drugs is effective in slowing or preventing the disease. "It's an incredibly important question," says Madhav Thambisetty, chief of the clinical and

Hallmarks of Alzheimer's in the Brain

Established signatures of Alzheimer's include amyloid plaque, tau tangles, and neuritic-plaque tau. Microglia cause trouble in later disease stages by triggering an inflammatory state that leads to tau buildup, the dying of neurons and cognitive decline.



translational neuroscience section at the National Institute on Aging (NIA) and a neurologist at Johns Hopkins University.

Two ongoing phase 3 drug trials intend to answer the question. The AHEAD 3-45 trial is testing the impact of lecanemab on the onset of clinical symptoms in people who currently have plaque but no symptoms; the TRAILBLAZER-ALZ 3 trial is doing the same with donanemab. Both trials are planned to run through 2027.

Genetic testing, too, will be part of the diagnostics picture for Alzheimer's. Patients can already be tested for the APOE4 gene. About one out of four people have one copy of the gene, which more than doubles the chances of developing Alzheimer's, and one in 40 or so people have two copies, leading to roughly a 10-fold increase in risk. Researchers have also found APOE4 variations that appear to confer a lower risk of the disease.

Over time, other genetic predispositions or protections from the disease are likely to emerge, and some may also lead to new drug targets and therapies.

Some researchers also point out that the hunt for ever-earlier signs of impending cognitive decline from Alzheimer's, while a boon to research and early treatment, requires consideration of privacy and medical ethics issues. Other concerns with genetic and other testing for very early Alzheimer's include the risk that the results could impact eligibility for employment, life insurance and long-term care.

Attacking the disease

The drug treatments that attack plaque are going to become increasingly effective, insist most researchers. Now that two anti-plaque drugs have been proven to slow the progress of cognitive decline, researchers and pharmaceutical companies can focus on new, better ways of hitting plaque. That may include new anti-plaque monoclonal antibodies that do a better job. Or it may be pills that work about as well but, unlike most antibodies, don't need to be 'infused' into patients—a biweekly or monthly process in which the drug is slowly dribbled into the body through an intravenous tube, usually in a clinic setting, or sometimes at home with the help of a trained caregiver.

Eli Lilly, for example, is developing a monoclonal antibody called remternetug that in early trials appears effective against plaque and may also be easily injectable under the skin like a flu shot.

Whether through existing anti-plaque drugs or new ones, researchers expect to see more patients

get more benefits as research and clinical experience help find ways to match the right drug to the right patients, and to zero in on the optimal doses and timing.

If there is a cloud hanging over the prospects for anti-plaque treatments, it is amyloid-related imaging abnormalities, or ARIA. ARIA are essentially small bleeds and minor swelling in the brain, first noticed more than a decade ago in MRI scans of patients who were taking some of the first experimental anti-plaque monoclonal antibodies (and also in some patients who were taking placebo). ARIA have continued to show up in a significant portion of patients in trials for these drugs. In most cases there are

“Little by little we'll approach the point where we can bring the cognitive decline to a full stop.”

no symptoms or only mild ones such as headaches that usually clear up within a few months, but there have sometimes been serious events such as seizures, strokelike symptoms and even death. For that reason, lecanemab carries an FDA “black box” warning, reserved for only drugs with the most serious concerns.

Few researchers suggest that worries over ARIA merit halting the use of anti-plaque drugs, given how welcome the progress in treatment has been to the Alzheimer's community and how dire the consequences of leaving the disease untreated. In addition, clinical trials are conducted on elderly patients with many comorbidities that can obscure the cause of symptoms. Still, many are calling for more research. “We have to try to understand the underlying mechanisms of ARIA,” says Wilcock. “And we're in desperate need of biomarkers that would help us identify the patients at highest risk.” Ultimately, she says, it should be possible to identify each individual's chances of being helped by an anti-plaque drug, along with the risk of being harmed, so that doctors, patients and families can make informed decisions about whether taking the drug makes sense. And hopefully drugs to prevent or dampen ARIA will emerge, she adds.

While anti-plaque strategies have been front and center when it comes to finding treatments for Alzheimer's, another important approach has been gaining more attention recently. It involves going after the so-called tau tangles that spread through the brains of Alzheimer's patients, particularly in the later stages.

Tau is a type of protein normally found within neurons, or brain cells, helping them to maintain their structure. But in Alzheimer's disease these proteins detach, deform and stick together into tangled forms that ultimately damage the neuron. Although the exact mechanisms of Alzheimer's remain cloudy, most researchers suspect that the buildup of plaque happens earlier in the disease, and the accumulating plaque eventually accelerates or even causes the formation and spread of tau tangles throughout the brain. Scientists used to think that amyloid and tau were competing theories but now believe they are part of the same disease cascade—that amyloid comes first and lays the groundwork for the formation of tau tangles, which is roughly when symptoms begin to emerge.

Evidence suggests that it is the tau tangles, more than the plaque, that directly cause cognitive decline. That theory received a boost from the trial for the experimental anti-plaque drug donanemab. The trial showed that the drug did more to slow cognitive decline among patients who had plaque but did

not yet have high levels of tau tangles—patients saw progression of the disease slowed by up to 60 percent.

The implication of that finding is that reducing plaque can slow the accumulation of tau, but once tau has sufficiently accumulated reducing plaque alone may be not effective. “We’re already seeing a sequenced approach in drug trials, where first you try to clear out the plaque and then inject an anti-tau drug,” says Gauthier. “I suspect within two years we’ll see an effective anti-tau drug and within three years this will be the normal sequence of treatment for patients.”

Although plaque and tangles are the main targets of Alzheimer's drug development efforts, other factors are known to play a role. Two of the biggest are brain inflammation and brain bleeding from damaged blood vessels. It isn't known whether these factors become part of the disease, are risk factors for it, or are simply independent factors that exacerbate and accelerate cognitive decline.

Regardless of their relationship to the disease, researchers believe attacking these problems will give Alzheimer's patients better outcomes. That means ultimately that patients will likely be treated with a combination of drugs.

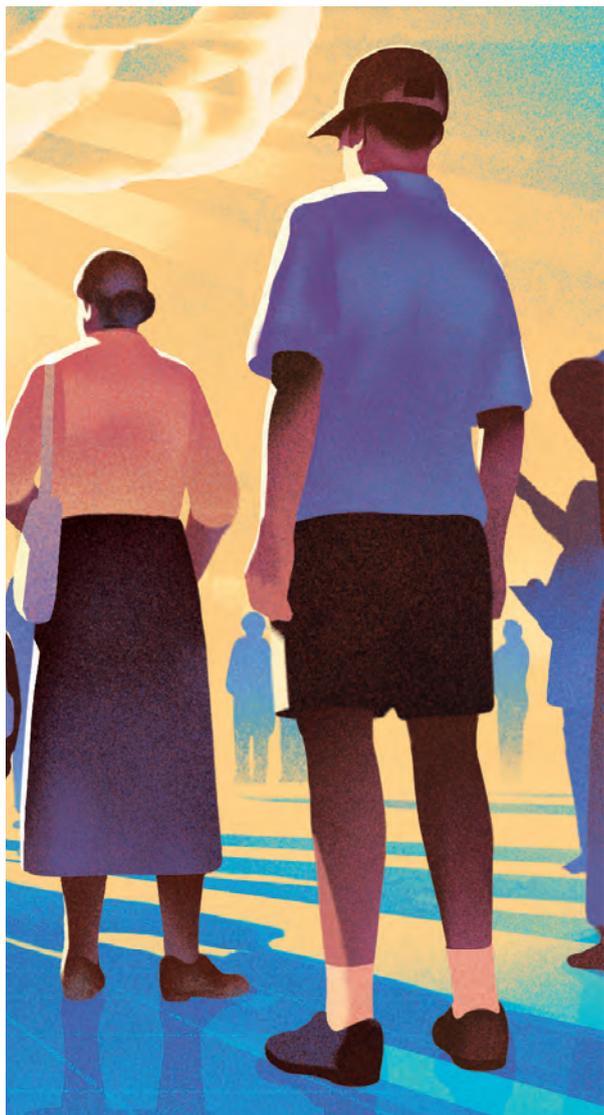
“In 20 years, we'll give patients different drugs for plaque and for tangles, and maybe each will slow the decline by 25 percent or more,” says Wilcock. “Then we'll give them something for inflammation, and maybe that will slow it by another 20 percent. Then we'll go after the health of their blood vessels and get another 15 percent. Little by little we'll approach the point where we can bring the cognitive decline to a full stop.”

Disparities

Alzheimer's puts a tremendous burden on patients, their caregivers and society at large. Patients lose years of productive life. Caregivers often sacrifice income to care for their loved ones who have the disease and their own mental health. All this has a huge impact on the world's capacity to be productive—a trend that will only increase as populations age.

Medicine may soon be able to help by dramatically slowing or even halting the progression of Alzheimer's. That raises concerns about how to get treatments to the people who most need them.

One concern is cost. In the U.S., most insurance plans will cover treatments, but deductibles, co-pays and caps will typically leave patients looking at many thousands of dollars in out-of-pocket costs. Only a fraction of the estimated 1 million patients in the U.S. who could qualify for treatments are likely



to be able to afford them. In addition, some groups that are more likely to get Alzheimer's disease, including Black Americans and Hispanics, also tend to have less access to adequate healthcare and to financial resources for covering out-of-pocket costs.

"This is an incredibly expensive disease," says Rabinovici, "and we're seeing disparities for minorities in every aspect of it, from inclusion in drug trials to access to specialty care. All of us involved in research and clinical care need to think about this and issue a collective call to action."

The U.S. healthcare system is already struggling with a shortage of clinicians, both primary care and

"We're seeing disparities for minorities in every aspect of [Alzheimer's], from inclusion in drug trials to access to specialty care."

neurologists. That's leaving many experts worrying how the system will cope with a growing number of Alzheimer's patients, combined with a new diagnostic and treatment protocol that will demand more time and expertise on the part of clinicians. "We're already scheduling patients six to 12 months out in our memory clinic, and we're turning many away," says Jeffrey Burns, a neurologist who co-directs Alzheimer's Disease Research Center at the University of Kansas Medical Center. "That's only going to get worse, especially as we develop ways to treat the disease earlier and earlier on and more patients push for those treatments."

Burns's center has pulled together tools that help train clinicians in how to help patients more effectively and efficiently and has recruited hundreds of primary care and other doctors and nurses into a support network to provide access to the tools and facilitate information sharing. Those types of supports will help, but Burns recognizes it will be a struggle to scale them up. "The challenges are magnified by the fragmented way our healthcare system is structured," he says. "Different hospitals and practices use different medical-record systems and have their own care protocols."

The U.S. public-health system, too, is fractured. The Centers for Disease Control and Prevention can issue centralized guidance, but actual public-health policy and programs are developed and implemented at the state or even local level. That disconnect will pose another obstacle to managing Alzheimer's, asserts Heather Snyder, a molecular biologist who

serves as the vice president of medical and scientific relations for the Alzheimer's Association. That's because coping with Alzheimer's will require more than just better treatments for individual patients, Snyder explains. "It's also going to take public-health actions that can impact behaviors at the population level," she says.

That means raising awareness of the warning signs of the disease and the need to have a conversation with a physician about them, she says. It also means finding ways to get more people to adopt healthy lifestyles and follow doctors' advice in order to limit heart disease, obesity, diabetes, and other chronic diseases to help prevent Alzheimer's. To help, in 2023 the Alzheimer's Association organized a summit in Atlanta of public-health experts and officials. "We need to engage state officials in thinking about how to bring the right risk-reduction messaging to the population," says

Snyder. "There's a lot of work to do." To compound the challenge, preventive medicine has long been a weak point in U.S. healthcare.

Issues of access are even more acute in poor nations whose healthcare systems struggle with less challenging diseases. "The kinds of healthcare resources we have in higher-income countries like the U.S. aren't available in many countries around the world, including brain imaging and neurologists," says Rabinovici. Not all healthcare systems around the world will make new anti-plaque and other Alzheimer's drugs available, or cover most of its costs, experts say.

Some pilot programs are addressing various ideas of getting healthcare to Alzheimer's patients. In Scotland, a pilot program funded by the Davos Alzheimer's Collaborative (DAC) is beginning to include blood tests and digital-cognitive tests into the regular checkups and national health systems. In Armenia, as part of another DAC-funded program, health workers who go out in vans to administer routine checkups will soon have blood tests and digital assessments.

In spite of these many concerns, the overall feeling in the field is that things are finally moving fast in the right direction. "This is an incredibly hopeful and exciting time," says Wilcock. "For the 24 years I've been in the field we've been telling patients that treatments were five years away. Now we can finally say we're here."

David H. Freedman is a freelance writer.

Stopping Alzheimer's Before Symptoms Appear

Scientists are investigating a strategy of “secondary prevention,” in which drugs given early on stave off cognitive decline.

BY DAVID H. FREEDMAN

While there are plenty of things that teenagers worry about, dementia isn't normally one of them. Yet one new major Alzheimer's drug trial is recruiting people as young as 18 to answer what may be the most pressing question facing the field: Can the ravages of the disease be prevented by identifying those on track to get it and treating them up to 10 years before they show symptoms?

The recent arrival of drugs that slow the cognitive decline of Alzheimer's in many people is a welcome breakthrough, but so far their efficacy has only been demonstrated in people with mild symptoms. By the time patients are diagnosed, their brains have already undergone extensive changes. But growing evidence suggests that taking the drugs well before that damage has occurred could significantly slow the disease and possibly even stop it in its tracks.

“Now we have drugs that can slow the disease by 30 percent or so in



people with symptoms, but that's not good enough," says Reisa Sperling, a neurologist who heads the Center for Alzheimer Research and Treatment at Brigham and Women's Hospital in Boston. "We want to get to 100 percent, and that means preventing people from getting to the symptomatic stages."

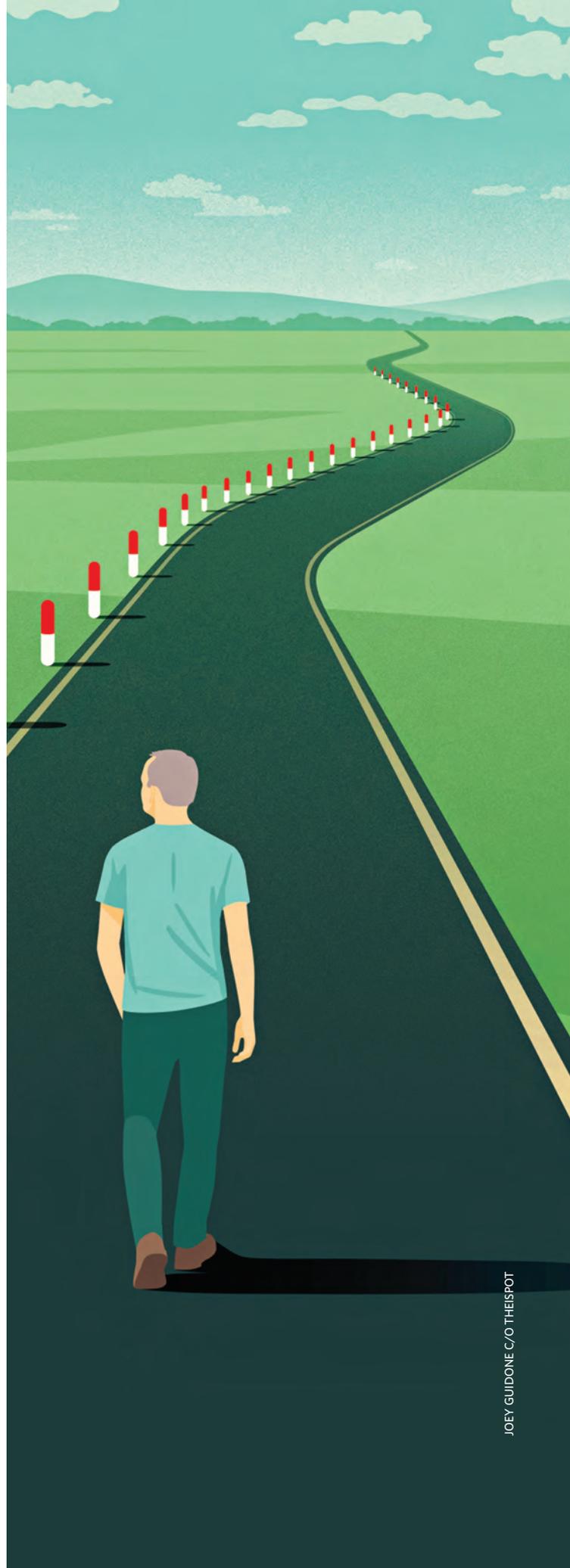
Earlier and earlier

In medicine, treating a disease when it is causing pathological changes in the body, but hasn't yet progressed far enough to cause clinical symptoms, is known as secondary prevention. (Primary prevention is heading off a disease before there is any pathology, and tertiary prevention is managing symptomatic disease to slow the worsening of symptoms.) Secondary prevention has been essential to medicine's triumphs in reducing the risks of death and disability for those with early heart disease or diabetes. Doctors don't wait for someone to have a heart attack before prescribing a cholesterol-lowering statin or for someone to suffer artery or kidney damage before putting them on metformin to control blood sugar.

In 2023, the results of trials of lecanemab (brand name Leqembi) and donanemab on Alzheimer's patients with mild cognitive impairment suggested that medicine may now have the tools to bring secondary prevention to bear on the disease. Both drugs are monoclonal antibodies that target the hardened clumps of protein called amyloid plaque that form in the brains of Alzheimer's patients.

Although much is still unknown about the mechanisms of Alzheimer's, there is little question now that the buildup of plaque precedes symptoms by many years. In the lecanemab and donanemab trials, the earlier patients were along the long road to plaque buildup, the better the drugs did in removing most of the plaque and slowing cognitive decline. "It's when you remove nearly all the plaque with one of these drugs that you see the real benefits in terms of symptoms," says Randall Bateman, a physician and professor of neurology at Washington University School of Medicine.

Because patients with even mild symptoms already have a large buildup of plaque, testing the notion that plaque-fighting drugs can be more effective earlier in the buildup process means enlisting presymptomatic patients for trials. "Studies are moving toward people who are just at the borderline for being positive for plaque and treating them to try to keep them from accumulating more of it and from having symptoms," says Susan Abushakra, a physician and researcher who is vice president of clinical



JOEY GUIDONE C/O THEISPOT

development and medical affairs at Alzheimer's-focused biotech company Alzheon in Framingham, Mass.

Three past trials have already focused on presymptomatic patients. One was the A4 study run by Brigham and Women's Sperling, which ended in 2020 after six years. It looked at the effect of the anti-plaque drug solanezumab on patients without cognitive impairment, but in whom PET imaging revealed some buildup of plaque. The other was the DIAN-TU study, headed by Washington University's Bateman, which studied the effect of solanezumab or gantenerumab, another anti-plaque drug, on pa-

The A4 and DIAN-TU studies received funding from GHR Foundation, which was also involved as lead philanthropic funder in the other trials as well. "Philanthropy can play a distinct catalytic role in this kind of visionary research," says GHR CEO Amy Goldman. Drug companies may hesitate to plunge into risky trials because shareholders want more certainty; and NIH and other public funding, while substantial, sometimes comes with administrative overhead. Philanthropies can change the game. "We're willing to take risks and provide the seed money to get a trial started, and we can be patient with long-term, com-

tients with confirmed plaque buildup are underway. One is AHEAD 3-45, also run by Sperling, which will test the effect of lecanemab on patients as young as 55 and as old as 80. The four-year-long trial will actually comprise two sister trials, A3 and A45. A3 is a phase 2 trial that will focus on people with lower levels of brain amyloid, while A45 is a phase 3 trial in which subjects have higher levels. In addition, A3 aims to measure the progression in amyloid while A45 will focus more on the onset of cognitive impairment. "All the data are pointing in the direction of getting better results by treating patients earlier in the disease, but now we need to prove it," says Sperling.

Another presymptomatic study is the TRAILBLAZER-ALZ 3, which will test donanemab on subjects with amyloid plaque but no signs of cognitive impairment. One relatively unique feature of the trial is that it will try to minimize the inconvenience to subjects, who would normally have to go to select hospitals to have brain scans and periodic in-person cognitive assessments. TRAILBLAZER-ALZ 3, in contrast, will rely primarily on easily administered blood tests and on telephone-based cognitive assessments. Reducing the subject burden in these ways is expected to make it much easier in Alzheimer's trials to enroll larger numbers of patients and to reduce the dropout rate. Like the AHEAD 3-45 trial, TRAILBLAZER-ALZ 3 will run through 2027.

A third study—an additional branch of the DIAN-TU trials—is aiming for a still-earlier intervention. That trial will test the effects of lecanemab on 230 subjects as young as 18. Because those patients carry the family genetic mutation that makes it almost certain they will develop symptoms of Alzheimer's by middle age and

"When we first started talking about doing a prevention trial in 2008, people thought we were nuts for wanting to put healthy people in that long a study."

tients who carry a rare familial genetic mutation that puts them at extreme likelihood of developing Alzheimer's and starting cognitive decline in their 30s, 40s or 50s.

The third trial was the Alzheimer's Prevention Initiative ADAD Trial, which also studied presymptomatic carriers of the familial early-onset mutation. ADAD took place in Colombia, and used the Genentech amyloid-clearing drug crenezumab. The eight-year trial ended in 2021. "When we first started talking about doing a prevention trial in 2008, people thought we were nuts for wanting to put healthy people in that long a study," recalls Eric Reiman, a physician and neuroscientist at the University of Arizona and Arizona State University and executive director of the Banner Alzheimer's Institute, which ran the ADAD study.

plex trials with a high potential for failure, especially with trials like these where there's also high potential for impact." Goldman says. Ultimately, the trials are typically funded by public-private philanthropic partnerships.

The three trials failed to find significant benefit to patients. But scientists don't interpret the findings as counter to the idea that anti-amyloid drugs, if given early enough, could potentially prevent cognitive decline. The drugs tested in all three trials work by different mechanisms than the newer drugs lecanemab and donanemab and never reached the same stages of regulatory approval. The newer drugs are now regarded as much more promising. In fact, the DIAN-TU trial is being extended with lecanemab.

Armed with the newer drugs, new trials on presymptomatic pa-

most likely by the time they are in their late 30s, the trial provides a chance to see the effects of treating the disease two decades or more ahead of the first symptoms.

Technically, this very-early-intervention DIAN-TU trial is addressing primary rather than secondary prevention, because the brains of these young subjects don't yet show signs of Alzheimer's pathology. But the results are likely to apply to secondary prevention, as well as to patients without the mutation, says Bateman. "In every study we know of, the results have lined up between people with the mutation and people with the sporadic form of the disease," he says, referring to the more common, later-in-life course of Alzheimer's. "It's highly likely the results of this trial will inform all of Alzheimer's."

Banner's Reiman is also planning a new ADAD trial using either lecanemab or donanemab. "Now that those drugs have been studied in amyloid-positive people with mild cognitive impairment, the fact that they work means they're almost certainly going to work in cognitively unimpaired people," he contends.

Faster trials, better treatments

One reason that effective Alzheimer's treatments have been so long in coming is that the slow course of the disease, and in particular the long lag between the early buildup of plaque and clinical symptoms, has made drug trials especially slow and costly. Identifying presymptomatic patients with plaque buildup has required PET scans or sampling spinal fluid, and determining whether a drug works on them has required watching them for years for symptoms that can be hard to assess.

But the prospects of drug trials on presymptomatic people

may be transforming, experts say. Plaque buildup can now be confirmed with blood tests, making it much easier and inexpensive to screen potential trial subjects. In a February 2024 paper in *Lancet Neurology*, Reiman and four colleagues argued that secondary prevention therapies could be approved for widespread use in three to five years and that blood biomarker tests will be able to be used to determine who is eligible.

In addition to new anti-plaque drugs, a second strategy is picking up momentum in the field: tack-

"These are early days, and we're still learning a lot. But from everything I know, I think these treatments are likely to work."

ling the tangles of tau protein that form in the brains of Alzheimer's patients around the time symptoms emerge. One theory gaining prominence in the field is that the long buildup of plaque eventually triggers or accelerates the formation of tangles, and it is the tangles that primarily cause the emergence and worsening of cognitive decline. Several anti-tau drugs are now in trials. Yet another new arm of the DIAN-TU trial will be testing three of them with Alzheimer's patients, in some cases combining them with anti-plaque drugs. Sperling, too, is planning a trial where patients will be treated with both anti-amyloid and anti-tau drugs.

Sperling notes that side effects of the anti-plaque drugs—particularly the risk of small-stroke-like

brain bleeds that show up in a small percentage of patients—remain a concern. So does the cost of treatment, currently running more than \$2,000 a month for lecanemab, plus the cost of administering the drug intravenously and closely monitoring patients who receive it. But she's confident the costs will come down—injectable versions of the drug, which are much easier to administer, are already in the works—and that further research will allow reducing the risks of side effects. "We need to be able to predict and prevent those events," she says.

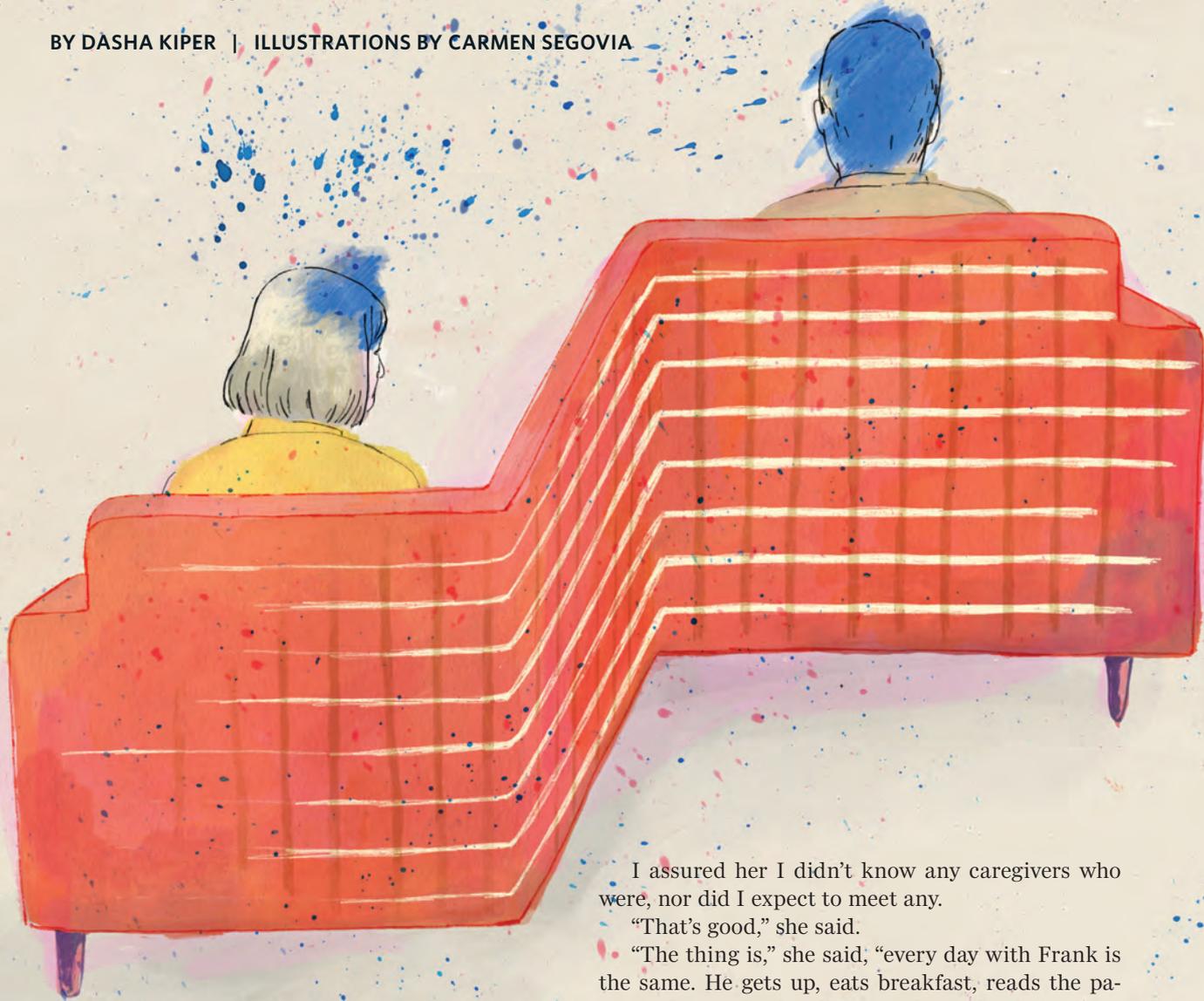
Noninvasive therapies are also being developed to preserve brain health. For instance, Cognito Therapeutics is developing a headset that uses sensory stimulation (light and sound) to provoke gamma-wave activity in the brain, which plays a role in learning and memory and is altered in Alzheimer's patients.

Before founding Cognito in 2016, Ed Boyden and Li-Huei Tsai of MIT confirmed in preclinical models that provoking gamma-wave activity with sensory stimulation can slow the rate of Alzheimer's disease progression. In later phase 2 trials, patients experienced a 69 percent slowing of brain volume loss and a 77 percent slowing of functional decline compared to a control group. A recent MRI study of the trial participants suggests that the device's combined visual and auditory stimulation reduces white matter atrophy and myelin loss, which help modulate neuronal network function. (Cognito is funded by in part by Morningside, a sponsor of this special edition, Alzheimer's Drug Discovery Foundation, X Ventures, and other firms.) The findings suggest that nondrug interventions may also play a role in secondary prevention of Alzheimer's. —**DHF**

“You should know, I’m not a saint.”

Most caregivers of people with Alzheimer’s find themselves behaving in ways they know are counterproductive. The disease affects their brains, too.

BY DASHA KIPER | ILLUSTRATIONS BY CARMEN SEGOVIA



Cathy is a woman in her late sixties, with a warm, tremulous voice. For six years, she had been taking care of her husband, Frank, who has Alzheimer’s. Recently, she had begun to berate herself for not being “cut from the same cloth as Mother Teresa”.

“You should know, I’m not a saint,” she said the first time we met.

I assured her I didn’t know any caregivers who were, nor did I expect to meet any.

“That’s good,” she said.

“The thing is,” she said, “every day with Frank is the same. He gets up, eats breakfast, reads the paper and naps. In the afternoon he grabs the remote, plants himself in his favorite chair, and turns on a game. If it isn’t the Mets, it’s the Jets. If it isn’t the Jets, it’s the Rangers or the Knicks or the Giants. And he’s not a passive spectator. Not Frank. He thinks he’s sitting above the dugout, and when someone fumbles a ground ball or misses a tag, Frank is on his feet, screaming at the poor guy. Or else, he’s leaning forward, predicting loudly when someone will screw up. ‘Don’t do it!’ he’d yell. ‘Wait! Wait!’”

If it isn't sports, it's a movie, any movie—that, too, presents an opportunity for Frank to participate. He yells at the actors, warning them of some impending disaster. Or he forecasts some dire plot twist, shaking his fist at the TV. And if an attractive actress shows up, he might suddenly shout, "That woman is about to take her top off! No one wants to see that!"

For months Cathy had put up with Frank's behavior even though his impromptu yelling and ridiculous predictions sucked the joy out of being in the same room with him. But when he became fixated on thieves attempting to break into their house at all hours of the day and night, insisting that she lock the doors and shut all the windows, she had had enough. Her patience and good will had run out.

"No one is out to get you!" she shouted one night. "No one wants anything from you. No one is looking to break in. You hear me? You have dementia! Dementia!"

Cathy knew, of course, that she shouldn't argue, that it was pointless to use logic and contradict her husband, but she couldn't help herself.

"I always thought I was a sensitive person," she mused. "Now I've become someone who kicks people when they're down. I tell him Errol Flynn isn't going to die. I tell him Doris Day isn't going to take her blouse off. I tell him he has dementia. Why do I do that?"

Cathy is not alone. The vast majority of caregivers know full well that their spouses or parents are ill, yet they still behave in ways they know are counterproductive: arguing, blaming, insisting on reality, and taking symptoms personally. Yes, Cathy understood that she was dealing with a disease, with someone suffering from delusions and hallucinations, but when Frank, panicked by imaginary thieves, refused to crack open a window, Cathy fumed with resentment, and that feeling gradually overcame her desire to be understanding and reasonable.

Telling me all this, she shook her head in disbelief. "You know, he's absolutely right. I don't blame him for getting angry," she said. "If someone had told me before Frank got Alzheimer's that my job was to agree with him and accept his reality, I would have said, 'Sure, what's so hard about that?' I mean, who cares that he thinks some jock is going to fall on his ass or that the weather girl is going to flash everyone? It's not his fault. Who does this?"

"Just about every caregiver I talk to," I said.

Although Cathy was taken aback by her own irrational behavior, it should not surprise us. Reasonableness is hardly our brain's first priority. The brain, after all, is an ultrasocial organ that has innate expectations that are often not met when caring for Alzheimer's patients. So when someone with whom

we've had a close relationship develops Alzheimer's, in many cases he or she begins to retreat into a world where we cannot follow. Not only do patients often not realize they have a neurological illness, they start speaking and behaving in ways that test our own sense of reality.

In Cathy's case, Frank not only stopped expressing nuance and self-doubt, he also lost his ability to see his wife as a complete person. Cathy had become a prop, a vessel into whom he could pour all of his fixations, and so she found herself living with a humorless stranger with whom she had nothing in common.

It's one of the heartbreaks of this disease. When someone we love develops cancer, patient and caregiver can commiserate, acknowledging the miseries of the disease while together experiencing, to some degree, a shared reality. But dementia at some point precludes this possibility. This strikes us as profoundly unfair because the collective reality that we once shared (and had come to expect) is now gone.

No wonder that unfairness leaves us feeling resentful. It's not because we don't get our own way, and it's not really about a shut window or who does the dishes. As social psychologist, Mathew Lieber-



man, explains, unfairness actually registers as a loss of social connection, and this feeling of isolation not only doesn't feel good, it does not bring out the good in us. This is why caregivers invariably bristle when confronted with memory loss, delusions, and loss of judgment. But where outsiders may view this as an irrational reaction to neutral, straightforward symptoms, caregivers like Cathy experience such symptoms as relentless reminders that the emotional reciprocity that had once existed between her and Frank had disappeared—and there is nothing remotely fair about that.

Indeed, such unfairness is tantamount to loss. And though we may understand this intellectually, we are biologically disinclined to accept this. This sense of isolation is not a metaphor or a conceit, but a neurological cross that many caregivers must bear. Human beings, after all, are built to experience threats com-

“When someone with whom we’ve had a close relationship develops Alzheimer’s, in many cases he or she begins to retreat into a world where we cannot follow.”

munally, through what psychologists call load sharing. As its name suggests, load sharing is a way of conserving energy by de-escalating anxiety and stress.

As a result, people in healthy and supportive relationships experience threats less intensely than those who feel isolated or alone. But this doesn't mean that every close relationship is necessarily beneficial. If, like Cathy, we're technically not alone but still feel alone, self-regulation becomes effortful, requiring mental energy that isn't always available. One might think that drawing on such energy with an intact prefrontal cortex is no great matter. But the right ventrolateral prefrontal cortex, where our “mental brakes” can be found, is not always able to exercise self-control.

Self-control is, in fact, a limited resource precisely because it's an effortful activity requiring the same kind of energy that our brain uses for any cognitive, physical or emotional activity, which means that there is precious little of it to go around. Every time caregivers like Cathy try to accommodate a patient's delusions, they apply mental brakes, which costs energy. Every time they struggle to keep their anger in check, they are hampered by the very people responsible for depleting the energy they need to maintain such control.

No wonder that after a long day of submitting to existential and mundane forms of unfairness, caregivers can become as volatile as the people they care for.

Dementia disorders create a physiological ensnarement that calls for mental energy even as it makes hitting those mental brakes increasingly difficult. So on top of the heartache and helplessness the disease brings, caregivers are also beset by guilt. They regard their inability to adapt to the disease as a character flaw, and many assume that their difficulties in accepting a patient's hurtful and frustrating symptoms is a matter of moral resolve, a question of will. If only they were “better people,” they tell themselves; if only they were stronger, more capable, more disciplined, they'd be able to handle better what the disease throws at them.

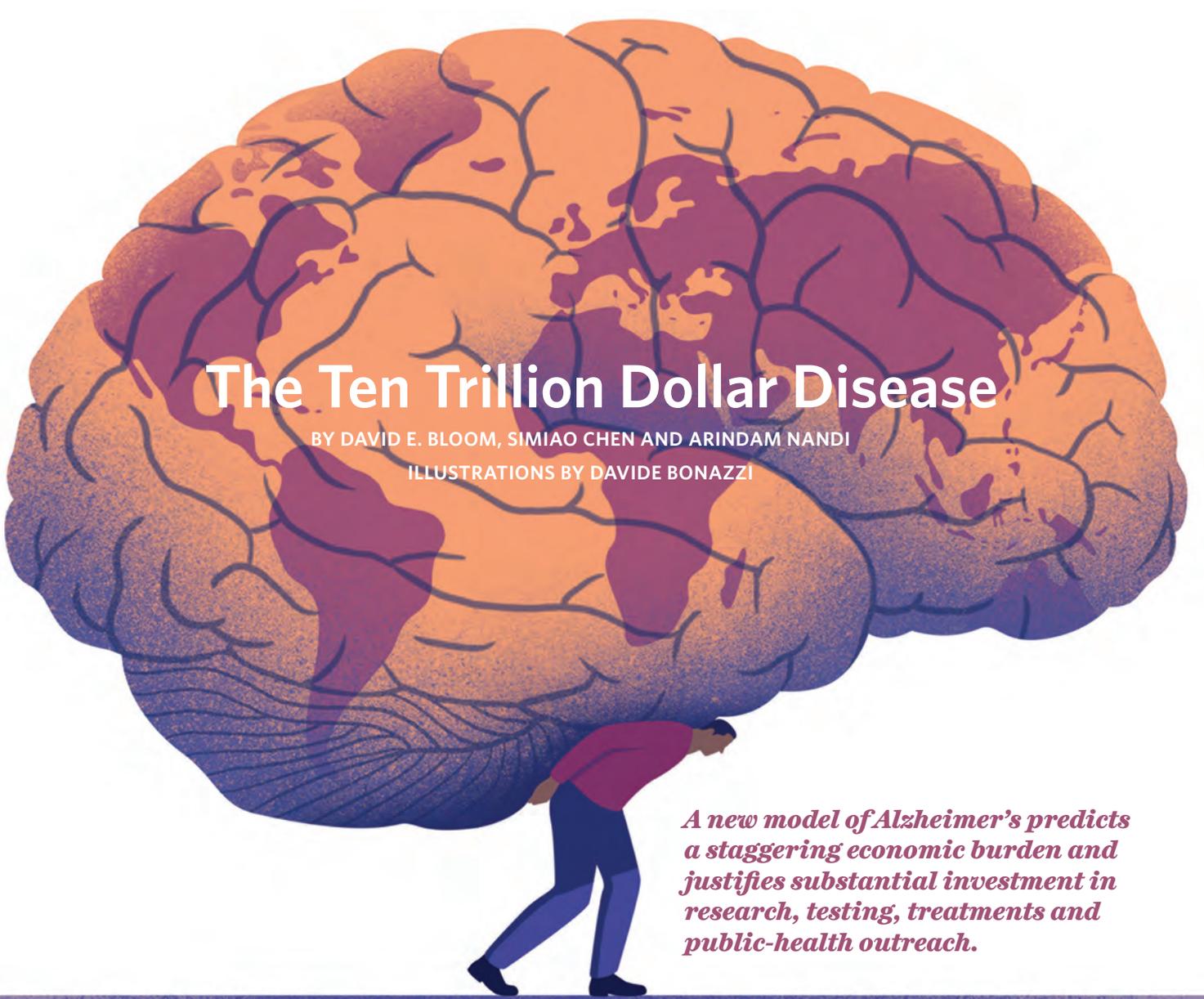
Sometimes the hardest part of listening to caregivers is knowing I can't assuage this guilt. When caregivers ask me what they can do to help them adapt, my response often surprises them because it has nothing to do with their loved one's mind, and everything to do with their own. I urge them to invest in their own brain, to understand that their behavior is not a matter of character weakness but a natural outcome of the healthy brain's limitations.

Most caregivers have only a very rough understanding of what the disease is doing to their own brains. It's important to let them know that their own physiology is part of the dynamic, forcing them to dip into those energy reserves required to accommodate strange and disturbing behaviors. Consequently, I urge them to give themselves a break, both figuratively and literally. I encourage them to take vacations, to spend time with friends, to find meaning and pleasure with people who can provide the reciprocity that is missing at home. By reducing their own stress, they will become better caregivers.

When I tell caregivers this, many of them nod politely but remain unconvinced. And even when they heed my advice and arrange to get away, their guilt rarely dissipates. In fact, self-care feels to them both counterintuitive and selfish. Why should they enjoy themselves when the person they care for has dementia and they're not “there for them.”

Given how inextricably connected our brains are with others, the more compassion and understanding we have for our own needs and limitations, the more energy we have to appreciate the needs and limitations of those who depend on us. Self-care is the only way a caregiver's mind can persevere.

Dasha Kiper is author of the book *Travelers to Unimaginable Lands: Stories of Dementia, the Caregiver and the Human Brain (Random House, 2023).*



The Ten Trillion Dollar Disease

BY DAVID E. BLOOM, SIMIAO CHEN AND ARINDAM NANDI

ILLUSTRATIONS BY DAVIDE BONAZZI

A new model of Alzheimer's predicts a staggering economic burden and justifies substantial investment in research, testing, treatments and public-health outreach.

Tremendous advancements in science, public health, and material standards of living in recent decades means that people are living longer than ever before. In 1950, when the world's population was 2.5 billion, life expectancy at birth was 46.5 years. In 2022, those figures rose to 8 billion and 71.2 years, respectively. By 2050, global life expectancy is projected to rise to 77.3 years.

This good news, however, presents a challenge: keeping many more older people healthy than ever before. By 2050, the number of people aged 65 and above is expected to reach 1.6 billion, up from 761 million in 2021, according to the U.N.'s World Social Report 2023.

Alzheimer's disease is one of the gravest threats to this growing population: as more and more people live longer and longer, the total number of people with Alzheimer's disease worldwide is expected to increase by more than 150 percent in the next 30 years. These people have progressively greater challenges in carrying out their day-to-day activities, are more likely to become injured from falls, and face major challenges managing otherwise straightforward medical problems. Many people with Alzheimer's disease suffer from hallucinations, confusion, and depression. It is also an ultimately fatal disease.

Alzheimer's disease can cause horrible suffering among patients and their caregivers. This suffering is part of the large burden Alzheimer's imposes on

people and their families, public-health systems, and nations. The economic cost of this burden is difficult to assess. It involves not only easily quantifiable effects such as treatment and long-term care costs and loss of work productivity and lifespan, but also myriad others that are not easy to measure, such as its effects on the mental health and livelihoods of caregivers and other indirect medical costs.

Quantifying the broad economic cost of Alzheimer's disease is important, not least because it is needed to assess the soundness of the expense to bring tests and, eventually, treatments to so many people through health systems. To this end, we have undertaken a comprehensive analysis, drawing on data from the Institute for Health Metrics and Evaluation (IHME), a leading research organization specializing in analyzing the global burden of diseases, as well as from other organizations and prior studies. We used a methodological approach that estimates the economic burden of Alzheimer's disease based on people's willingness to pay to avoid the risk of death. We also developed a macroeconomic model of the productive capacity of a country's economy that allows for a reduction in labor and capital formation resulting from the disease burden. These methods take into account a wide array of direct and indirect costs of Alzheimer's disease for individual patients, caregivers, and the aggregate economy.

Based on our willingness-to-pay approach, we estimate that the global economic burden of the disease in 2019 was roughly \$2 trillion. By 2050, that burden will rise sharply to about \$10 trillion and perhaps as high as \$13.5 trillion. For comparison, world GDP is projected to be \$228 trillion (inflation adjusted) in 2050.

The problem is especially urgent because the economic burden of Alzheimer's is projected to worsen global economic inequality. Although the current economic costs of Alzheimer's are concentrated in the wealthiest countries, these will grow much faster in low- and middle-income countries, which are less able to shoulder them. Between now and 2050, the number of people with Alzheimer's disease in Northern Africa, the Middle East, and Eastern Sub-Saharan Africa is projected to grow by 250 percent, compared to 150 percent worldwide.

The economic burden of Alzheimer's disease will be staggering and justifies a substantial scale-up of

investments: in R&D spending on Alzheimer's prevention, early detection, and disease-modifying therapies; the development of new modalities of care; and widespread, equitable access to these innovations. Experts in public health, medicine and policy are beginning to sound the alarm. They warn that massive investments are needed—not just for humanitarian reasons but also as wise economic policy.

The current toll

Disease burden research and estimates have typically focused on dementia, which, in addition to Alzheimer's disease, also includes vascular dementia, frontotemporal dementia, Lewy body dementia, among other forms.

Dementia is the sixth-leading source of disability burden among those aged 55 and older. Alzheimer's disease accounts for approximately 60 to 80 percent of this burden. Based on this proportion, estimates from IHME suggest that in 2019, 34 million to 46 million people around the world had Alzheimer's. Even if the age- and sex-specific prevalence of dementia remains stable in the coming years, population growth and rising longevity mean more people will be at risk of Alzheimer's disease. In this vein, the total number of people living with Alzheimer's disease is projected to rise to about 107 million by 2050. (For this estimate and some others in this article, we give the midpoints of projected ranges; in this case, the range was between 91 million and 122 million.)

Despite decades of research, medical interventions that substantially prevent, slow the progression of, or cure Alzheimer's disease are not yet available. While there are many successful models of coordinated care for people with Alzheimer's disease, they are not widely implemented. Most face difficult decisions about trying to receive care at home or living in a nursing home, both marked by hospitalizations and visits to the doctor.

A traditional method for tabulating these expenses is the cost-of-illness (COI) approach, which includes out-of-pocket medical and long-term care expenditures for patients and costs incurred by such payers as insurance companies or government-run healthcare systems. Globally, an estimated \$184 billion was spent in direct healthcare costs for people with Alzheimer's disease in 2019. By 2050, that number is projected to reach \$1.1 trillion per year. While

“By 2050, the burden of Alzheimer's disease will roughly grow fivefold to \$10 trillion and perhaps as high as \$13.5 trillion.”

high-income countries are expected to see direct costs from Alzheimer's disease multiply by a factor of five during this time, upper-middle income, lower-middle income, and low-income countries could see these COI estimates grow by factors of 21, 15, and 13, respectively.

A 2018 study using the cost-of-illness approach estimated the combined direct and indirect global costs of Alzheimer's, including costs associated with seeking medical care (such as transportation and meals), the value of lost economic productivity of patients and caregivers, the medical cost of treating dementia-induced events (such as injuries) and, finally, the cost of the mental suffering of caregivers. The authors estimated the combined direct and indirect global costs of Alzheimer's disease to be between \$575 billion and \$766 billion in 2015 and projected that it would increase to about \$6.4 trillion by 2050.

COI studies, however, have limitations. Most leave out what economists call "productive nonmarket activities," which include caring for grandchildren, volunteering in the community, and other unpaid activities that enrich lives. These activities are not measured traditionally in terms of wages or economic output and are rarely included in conventional estimates. In the U.S., 46 percent of a person's total lifetime economic output is estimated to come after the age of 60—about half of it from employment, half from unpaid activities. Because of lack of data, analyses of the cost of care for Alzheimer's disease, even if they include formal productivity losses for patients and caregivers, typically do not capture these nonmarket activities.

The economic costs of Alzheimer's disease go even further beyond the cost of treatment or long-term care, as we and our colleagues reported in *npj Aging* in February 2024. A patient may no longer be physically or mentally capable of being employed or be less productive at work, both of which can reduce their own earnings and, in turn, the aggregate economic output of a country. Moreover, in many communities, especially among low-income families that cannot afford expensive nursing homes or home visits by professional caregivers, unpaid caregiving by family members (especially women) remains the norm, likely exacerbating income inequality. In fact, as many as 94 percent of people with dementia in low- and middle-income countries such as Brazil, China and Costa Rica receive their care at home. To quantify the lost economic productivity of unpaid caregivers, some researchers have calculated op-

portunity cost (potential earnings of the caregiver if they were instead gainfully employed in the market), and others have calculated replacement cost (the economic value of an equivalent amount of care that could be given by a professional caregiver at home instead of the unpaid caregiver). For a person with dementia in the U.S., these indirect cost estimates range from 31 to 49 percent of the total cost of care.

Even considering the lost market productivity of informal caregivers, other factors contribute substantially to the total cost of Alzheimer's. Caring for people living with the disease is mentally and emotionally difficult for family members, but this pernicious impact is an indirect cost that is typically overlooked. Seeing your parent, grandparent or other loved one suffering from a debilitating disease like Alzheimer's can be heartbreaking. The caregiver is often a witness to changes to their loved one's personality and a deterioration of their memories—a

"The problem of Alzheimer's threatens to significantly worsen economic inequality."

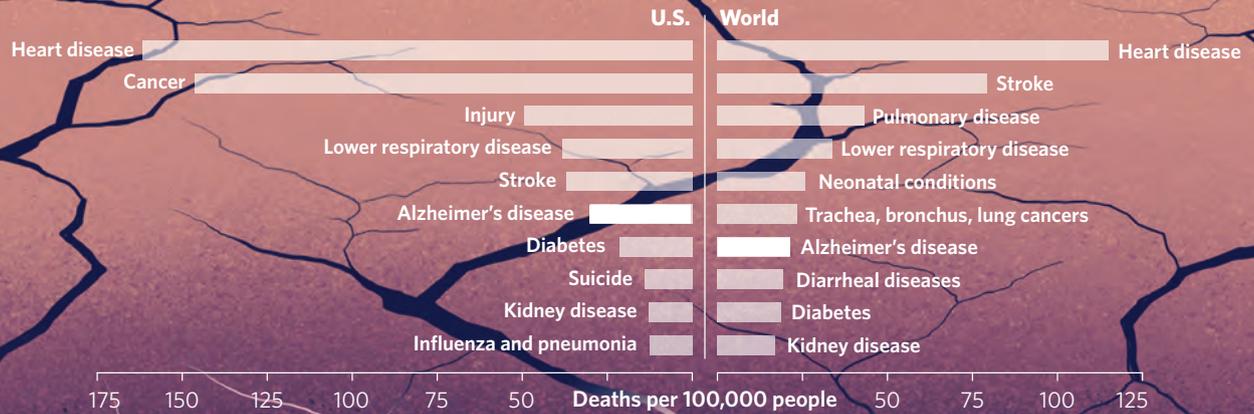
decline that often leads to the inability to recognize family members. A comprehensive assessment of the economic burden of Alzheimer's would include the toll on caregivers and other indirect costs.

A different way of looking at costs

Another method for measuring the potential economic burden of Alzheimer's is called the value-per-statistical-life, or VSL. The VSL measures a society's willingness to pay for lowering the risk of death. If a representative person were willing to pay \$100 on average for a 1 in 100,000 reduction in the probability of one's own death, it would take \$10 million paid by 100,000 such individuals to collectively avoid one death (or to save one "statistical life"). VSL reflects how individuals value their own lives, presumably encompassing various aspects of healthy living that may range from having a job and earning money to being physically and mentally active, enjoying a good book, a vacation, or spending time with loved ones.

The VSL approach to assessing the economic burden of Alzheimer's typically delivers estimates that encompass a broader range of value than estimates based on macroeconomic modeling or human capital and cost-of-illness approaches. But VSL-based estimates—like estimates based on these other methods—are subject to criticism.

Ten Leading Causes of Death



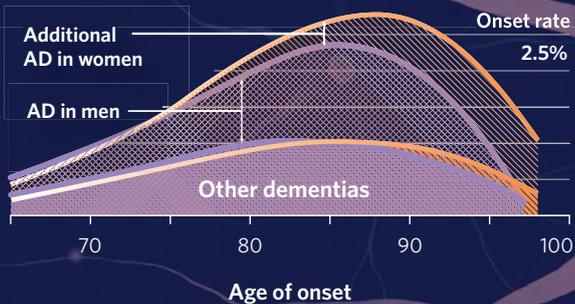
*2019 is the most recent year global data are available. In 2020, COVID was the third-leading cause of death in the U.S.
 Sources: J. Xu et al., National Vital Statistics Reports, Vol.70, No.8 (2021); "The top 10 causes of death," World Health Organization, December 9, 2020.

Alzheimer's Disparities by Gender



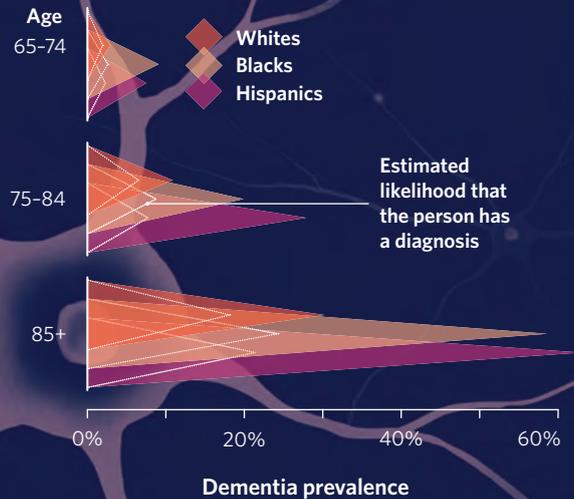
In the U.S., two-thirds of the 6.7 million people living with Alzheimer's disease are women.

In part the difference exists because women live longer. But one study found that at each age, other dementias have nearly the same prevalence in both genders, yet Alzheimer's appears more in women.



Source: "Race, Ethnicity, and Alzheimer's," Alzheimer's Association Fact Sheet, March 2020.

Alzheimer's Disparities by Race and Ethnicity in the U.S.



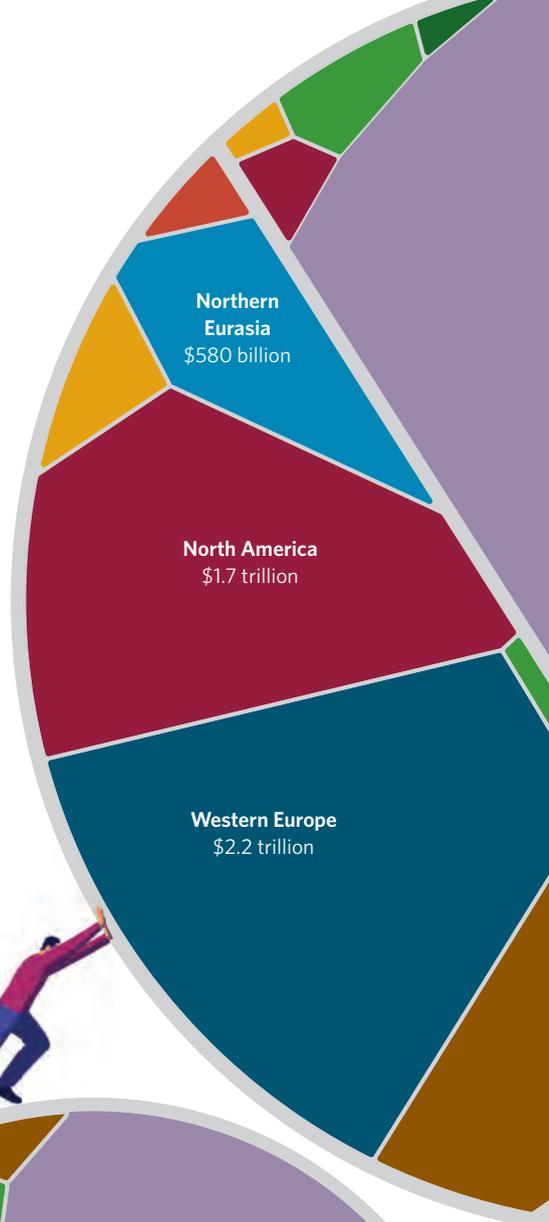
Source: C. Beam et al., *Journal of Alzheimer's Disease*, 64, 1077 (2018)

[INFOGRAPHIC]

The Ballooning Economic Impact of Dementia

New models predict that the cost of Alzheimer's and other dementias will grow sixfold by 2050.

As dementia skyrockets worldwide, so too will the costs to governments, healthcare systems, and economies. In 2022, David E. Bloom of Harvard and colleagues from the U.S., Canada and Germany published a study that modeled those costs to 2050. They considered the lost value of a statistical life—an economic metric that estimates what the public is willing to pay to reduce risk—for patients with dementia and projected that value forward in time as world populations grow and age. By mid-century, the financial burden of dementia will increase sixfold and shift from high-income countries to upper-middle-income ones. —Katie Peek



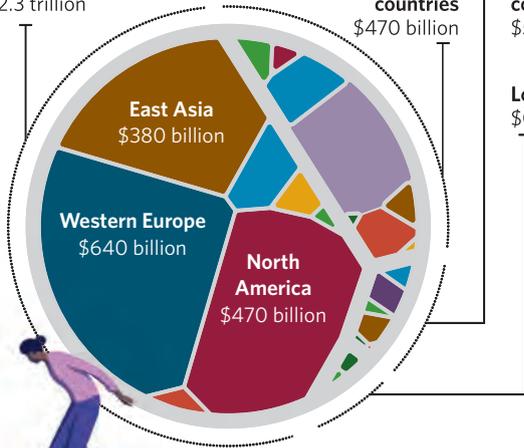
2019 \$2.8 trillion

High-income countries
\$2.3 trillion

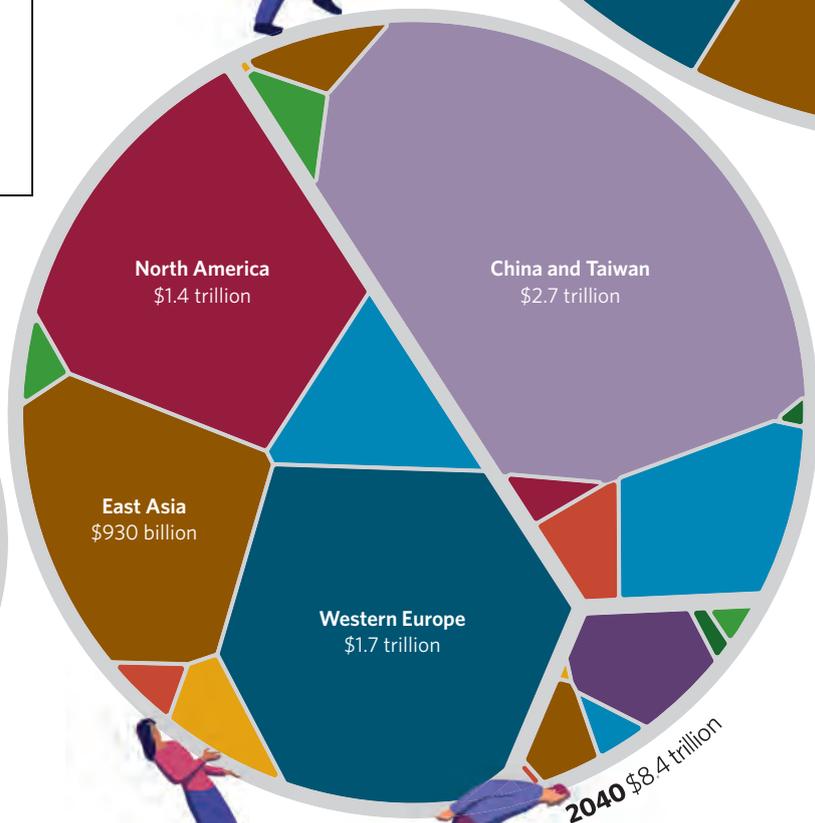
Upper-middle-income countries
\$470 billion

Lower-middle-income countries
\$54 billion

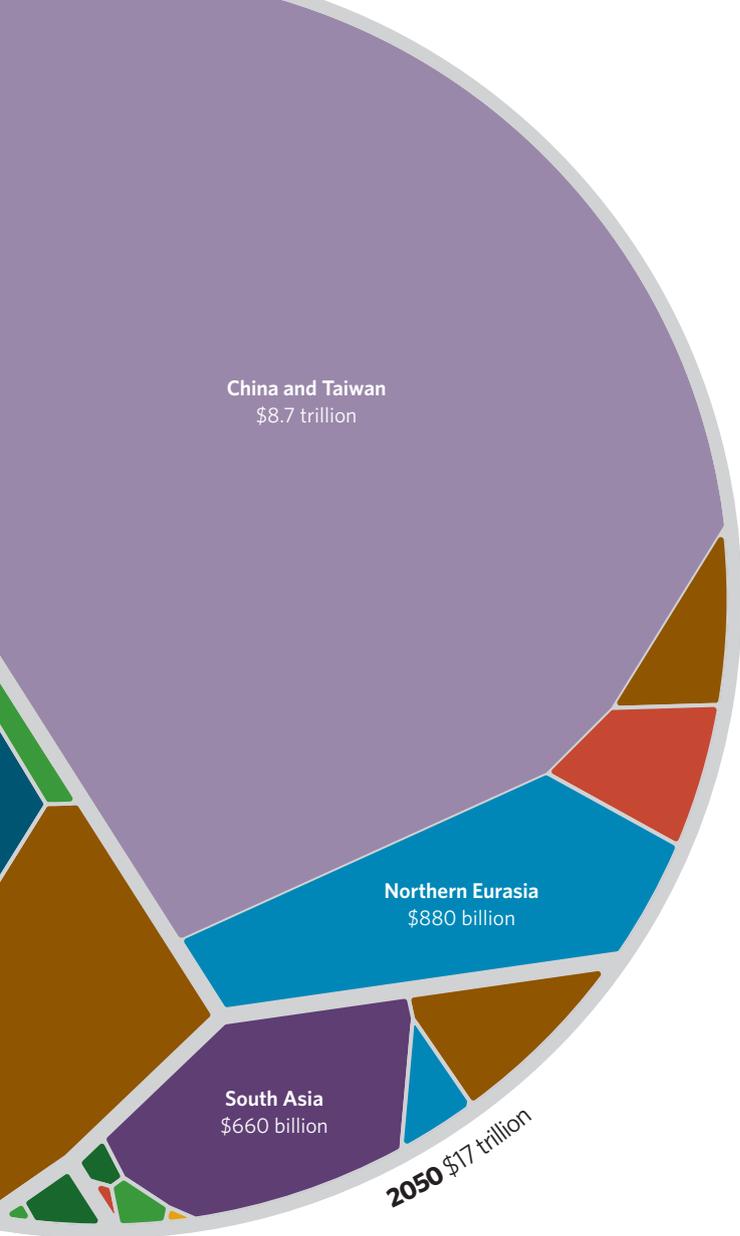
Lower-income countries
\$0.65 billion



2030 \$4.7 trillion



2040 \$8.4 trillion



KEY

Each circle represents the total economic burden—in 2020 U.S. dollars—of the years lost to Alzheimer’s and other types of dementia. The area of each segment represents the dollar value lost. Thick lines separate different income levels; segments within those areas are colored by world region. (The smaller areas are approximated.) Regions correspond to the colors in the map below.



Source: A. Nandi et al., *eClinicalMedicine*, September 2022, Vol.51:101580

One common criticism is that VSL-derived cost estimates increase with income, suggesting that the lives of people living with Alzheimer’s disease in relatively high-income countries are worth more than the lives of people living with Alzheimer’s disease in low- or middle-income countries. This ethically problematic property of the VSL approach arises from the fact that VSL is derived from people’s *willingness* to pay for relatively small reductions in mortality, which in turn reflects their *ability* to pay.

This criticism can be addressed in multiple ways, such as by assuming that the value-per-statistical-life year (VSLY)—calculated as VSL divided by the expected number of years of life remaining—is the same for all countries. Modifications like this, however, are atypical in the literature on this topic. To keep our estimates broadly comparable to those of other economists, we chose not to make this adjustment to the VSL estimates in the study reported in this article.

Another criticism of the VSL approach is that it does not include all costs of Alzheimer’s disease, such as those associated with informal caregiving, medical research, or medical care paid for by third parties. This issue can, however, be addressed by interpreting VSL estimates as underestimates of the true costs or by separately calculating the excluded cost components and adding them to the VSL figures.

In a recently published study in *eClinicalMedicine*, we adopted the VSL approach to estimate the economic burden of Alzheimer’s disease and other forms of dementia across 168 countries containing more than 99 percent of the world’s population.

In this study, we obtained data on disability adjusted life years (DALYs) lost to Alzheimer’s disease from a database prepared by the IHME Global Burden of Diseases study. A DALY represents the loss of the equivalent of one full year of healthy life. DALYs are calculated as the sum of the years of life lost for those who die from Alzheimer’s and the effective years of life lost for those who experience disability from the disease. The more severe the dementia, the more effective years of life are lost. For example, one year of living with severe Alzheimer’s is equivalent to 0.6 year of living without the disease, and one year of living with mild disease is equal to 0.93 year of living without it.

We then monetized each DALY lost to Alzheimer’s disease as being equal to VSLY. For instance, to calculate the VSLY for the U.S., we started by considering the VSL for the U.S., which various U.S. government agencies and researchers have estimated to be approximately \$10 million to \$12 million. (For other countries, VSL is typically derived by adjusting the

U.S. estimate for differences in income and purchasing power.) Based on standard life table estimates, a median-aged U.S. resident in 2019 would have a remaining life expectancy of 43 years. The VSLY figure for the U.S. comes to \$246,512 (\$10.6 million divided by 43 years). This figure represents the monetary value of each year of full health lost to Alzheimer's in the U.S., which can be interpreted to include the value of all measurable aspects of a healthy year of life, such as employment, as well as intangible aspects, such as enjoying leisure. It likely does not capture the full economic value of unpaid caregiving, which constitutes a large part of overall care costs for Alzheimer's.

We projected future VSLY values for each country based on average annual growth rates of gross national income per capita from 2010 to 2019. Based on these figures and our projections of Alzheimer's cases (which assume that Alzheimer's would continue to account for 60 to 80 percent of the future global burden of dementia, we estimate the global economic burden of Alzheimer's disease in 2019 to be about \$2 trillion. We also project that the global economic burden of Alzheimer's would rise to between \$2.8 trillion and \$3.8 trillion in 2030, to between \$5.1 trillion and \$6.8 trillion in 2040, and to between \$10.1 trillion and \$13.5 trillion by 2050. These estimates are reported in 2020 U.S. dollars, with future values discounted at the rate of 3 percent per year.

Our findings also show that the global center of gravity of the economic burden of Alzheimer's will gradually shift away from high-income countries, which currently have the greatest number of people with Alzheimer's and toward upper-middle-income countries, which will experience rapid growth in the number of older adults and, as a result, those living with Alzheimer's. Between 2019 and 2050, the VSL-based economic burden is projected to increase by a factor of 22 in upper-middle-income countries, as compared to 3 in high-income countries. The burden will also grow in other parts of the world at greater rates than in high-income countries, though their absolute magnitude in 2050 will remain low in comparison with upper-middle-income countries.

While the two approaches for assessing the economic burden that we've discussed thus far—the COI

method and VSL method—can reliably estimate the economic impact of Alzheimer's disease on people with the disease and their caregivers, neither account for its longer-term and aggregate macroeconomic effects. Deaths and disability from Alzheimer's disease diminish the size and productivity of the workforce, reducing national economic output.

Out-of-pocket care costs from Alzheimer's disease can significantly deplete household savings. These savings might otherwise have been invested in retirement accounts or used to support family businesses or the education of children or grandchildren. Costs incurred by health insurance companies trans-

“Good health confers follow-on economic and social benefits that need to be acknowledged and appropriately valued.”

late to higher insurance premiums and lower household savings for consumers. Similarly, costs paid by social healthcare systems may need to be funded by taxes that, in turn, reduce personal savings. Finally, diverting money to Alzheimer's care might reduce vital public investments in education, other aspects of health, and infrastructure development that generally have high economic returns.

Our macroeconomic model

To account for the effects of Alzheimer's disease on national and global economies, we developed a macroeconomic model that simulates the productive capacity of a country's overall economy. It accounts for the reductions in labor from Alzheimer's-related mortality and morbidity, both for patients and caregivers, and reductions in capital formation because of lower savings. It iteratively estimates the value of economic output based on the available labor and capital stock, part of which is then saved by households and invested as capital to spur future economic production.

We estimated that during the 2020-2030 decade, loss of labor and lower rates of capital formation would lead to a global macroeconomic cost of \$1.5 trillion. We project cumulative losses between 2020 and 2040 to be about \$4.3 trillion and losses from 2020



to 2050 to be about \$7.3 trillion. These estimates are conservative, however, in that they do not account for likely economy-wide technological progress, and they do not include the value of productive nonmarket activities of people with Alzheimer's disease.

Macroeconomic analyses provide a fundamentally different view from COI or VSL on the potential future economic burden of Alzheimer's disease. All take into account demographic and disease-burden patterns, but macroeconomic analyses also account for the underlying rates of household savings, capital formation, and average income in each country. Our macroeconomic analyses find that while low- and middle-income countries are projected to bear the largest health burdens—close to three-quarters of the DALYs lost to Alzheimer's disease by 2050—their share of the macroeconomic burden would remain just under 50 percent. As another example, South Asia would still account for 19.4 percent of the DALYs lost to Alzheimer's in 2050 but only 1.6 percent of the macroeconomic burden from 2020 to 2050, while North America would account for only 4.5 percent of the DALYs in 2050 but 28.5 percent of the economic loss from 2020 to 2050.

Like our willingness-to-pay (VSL) analysis, our macroeconomic burden modeling uses underlying disease-burden projections that differ from the latest IHME estimates. Our projections assume that the Alzheimer's disease burden would continue to grow in each country at the same rate as in the past (from 2010 to 2019). By contrast, IHME's estimates are based on a more detailed methodology that considers several contributing or risk factors for dementia, such as education level, physical activity, and exposure to air pollution. However, the IHME estimates are available only for 2050 and not the intermediate years that we evaluated. The IHME study also does not directly report the DALYs that are used in our analyses. Our linear projections of future Alzheimer's cases are slightly lower than IHME estimates: 133 percent between 2019 and 2050 versus 166 percent in IHME estimates. This suggests that our estimates of the economic burden of Alzheimer's disease may be relatively conservative. While our estimates may be limited by some uncertainty surrounding the future disease burden, they nonetheless present a strong economic case for investing in research to prevent and manage Alzheimer's disease.

To be sure, recent research has shown that wealth and health are a two-way street. Population health is a benefit of affluence, and healthy populations tend to have more vibrant and robust economies than their less healthy counterparts. Healthy populations also tend to be more stable, cohesive, equitable, and secure. Insofar as global societal well-being is driven by population health in a plethora of ways, the full benefits of population health need to be acknowledged and measured in the interest of efficiently allocating scarce public and private resources and garnering the biggest returns from them.

The combination of a rapidly aging global population and the lack of treatments for Alzheimer's is problematic now. In the coming decades, as the toll of the disease swells rapidly, it could become a significant impediment to human progress. In 2020, the U.N. General Assembly declared this decade as the Decade of Healthy Aging, calling upon governments, civil society organizations, the private sector, academic experts, and other stakeholders to join hands in improving the lives of older adults. It would be wise to act now.

David E. Bloom is Clarence James Gamble Professor of Economics and Demography at the Harvard T.H. Chan School of Public Health. Simiao Chen is an associate professor and head of research unit at Heidelberg Institute of Global Health at Heidelberg University. Arindam Nandi is a researcher at the Population Council. The following individuals are also coauthors: Zhong Cao (Tsinghua University), Nathaniel Counts (NYC Department of Health and Mental Hygiene), Maddalena Ferranna (USC Alfred E. Mann School of Pharmacy), Benjamin Seligman (UCLA David Geffen School of Medicine), Daniel Tortorice (College of the Holy Cross), and Daniel Vigo (University of British Columbia Dept. of Psychiatry and School of Population and Public Health). The Davos Alzheimer's Collaborative provided financial support, through a contract with Data for Decisions, LLC, for our original research described in this article.

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A Marathon Journey from Lab to Clinic

How 20 years of molecular detective work led to the first effective Alzheimer's drugs.

BY ESTHER LANDHUIS



On a spring day in 2011, neuroscientist Cynthia Lemere stood nervously before scientists gathered to appraise the world's latest research—including hers—at a conference on immune strategies for treating Alzheimer's disease.

Advancing her presentation slides to show stained brain tissue from a recent set of mouse experiments, Lemere circled the pointer around the reddish-brown clumps: protein fragments called amyloid beta that form plaques, a hallmark of the disease. In Lemere's experiments, mice that received antibody treatment accumulated fewer amyloid plaques than animals receiving placebo.

Some in the audience were skeptical. As Lemerere recalls, when she finished her presentation one prominent researcher rose and proclaimed: “It’s not a real thing. It’s a biochemical artifact.”

What that researcher dismissed, others pursued. Lemere and colleagues at Brigham and Women’s Hospital in Boston have studied this form of amyloid beta since the 1990s; so have researchers in Japan and Germany. Now, the rogue protein is center stage: A drug (donanemab) that targets the molecule recently showed clear benefits in a large clinical study of people with mild Alzheimer’s disease.

Donanemab’s success follows another Alzheimer’s drug, lecanemab (brand name Leqembi), which hit the market in January, and aducanumab (brand name Aduhelm), which got a nod from the U.S. Food and Drug Administration in 2021 after a controversial review. These are the first new Alzheimer’s treatments since 2003, and the only ones to impede the disease’s progression; earlier drugs only eased symptoms.

The new therapies are revitalizing Alzheimer’s research and renewing hope for millions of families touched by this devastating disease. Yet these treatments carry some risk and a formidable price tag. Translating them from controlled studies to clinical use will require diagnostics that are more scalable

and accessible, as well as new training to equip physicians to recognize early-stage disease and decide who is eligible for treatment.

Molecular underpinnings

Alzheimer’s is the most common cause of dementia. It afflicts nearly 7 million people in the United States and more than 30 million worldwide. Older drugs—including donepezil, galantamine and rivastigmine—work by prolonging the activity of key chemical messengers in the brain. This enhancement of nerve cell communication offers a temporary boost but does not get at the disease’s molecular roots.

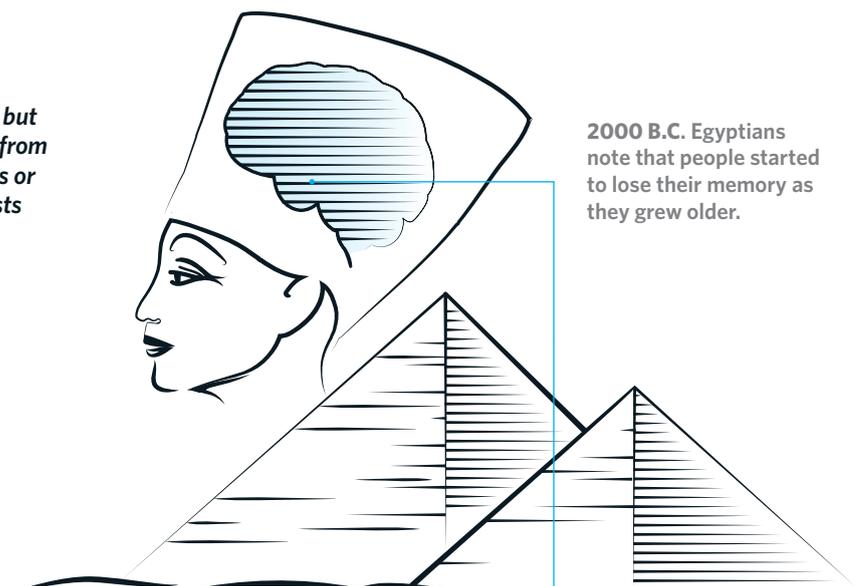
The newest drugs do. They are the long-awaited fruit of the amyloid hypothesis, the theory that identifies amyloid buildup as an essential trigger that disrupts neural circuits, causing mental decline and other signs of dementia decades later. This theory has driven much of the Alzheimer’s disease research and drug development since the 1990s.

Creating drugs to slow this progression requires a deep understanding of how the culprit molecules form and how they become a threat. Before amyloid clumps into disease-associated plaques, it floats in the blood as harmless proteins. Day by day, decade after decade, these amyloid beta peptides are churned

“Watching a neurodegenerative disease cause the slow decline of a loved one is sad, worrisome and exhausting”

A Brief History of Alzheimer’s Disease

Dementia has been around for eons, but scientists distinguished Alzheimer’s from other forms only in the last 100 years or so. Now effective treatments and tests are in development.



2000 B.C. Egyptians note that people started to lose their memory as they grew older.

Sources: Phyllis Barkman Ferrell; “Milestones” by the Alzheimer’s Association, https://www.alz.org/alzheimers-dementia/research_progress/milestones.

out and cleared out, like scores of other proteins processed in the brain as part of normal metabolism.

At some point, though, things go awry. Amyloid collects and forms clumps in the brain, eventually killing nerve cells and making it hard for people to remember things and manage everyday tasks such as paying bills and getting dressed. “Watching a neurodegenerative disease cause the slow decline of a loved one is sad, worrisome and exhausting,” says Lemere. She lost two aunts to a related condition, Lewy body dementia, and says that “definitely had an impact on my desire to keep working in this field.”

To study the progression of Alzheimer’s, Lemere and colleagues use laboratory mice that are engineered to mimic key pathological manifestations of the human disease. One example: the plaques stained reddish-brown on Lemere’s conference presentation slides.

Each clump represents amyloid beta, but these peptides are anything but identical. Some exist alone as monomers. Others assemble into menacing struc-

tures called fibrils, or as intermediate-sized oligomers, which many researchers consider to be the most toxic to nerve cells. Plaques can act as a reservoir for these smaller, toxic species.

What’s more, individual peptides differ in length and shape and sometimes morph further through chemical reactions, as shown in scores of biochemical

“Creating drugs to slow the disease’s progression requires a deep understanding of how the culprit molecules form and how they become a threat.”

studies. One variant—a ring-shaped molecule called pyroglutamate amyloid beta (pyroglu A β) is especially nasty. In lab studies decades ago, it seemed sturdier and stickier than other amyloid peptides and hurt nerve cells even at tiny concentrations.

These observations were later confirmed in therapeutics tested on mice and ultimately in clinical trials of Alzheimer’s patients—but it has taken decades to capture attention from the scientific community.

An intriguing culprit

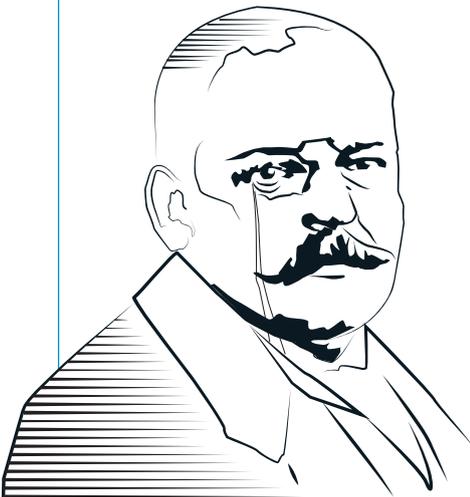
Initial descriptions of pyroglu A β appeared in the biomedical literature as early as 1985. Interest grew as multiple labs published follow-up papers confirming the presence of this unusual protein in autopsy tissue from Alzheimer’s patients. In some brain specimens Lemere analyzed in the 1990s as a Ph.D. student, pyroglu A β appeared as a dominant species.

In those analyses—when Lemere noticed that pyroGlu showed up well in some samples but less so in others—it seemed to depend on how the tissues were processed. When specimens sat in fixative solution for longer than a few hours, pyroglu A β was faint or undetectable, she says.

Methodological challenges like that plagued the field for years, fueling claims that pyroglu A β was a biochemical artifact.

There was another problem with pyroglu A β : No one could explain how it was formed. Then, in 2000, a doctoral student in Germany studying diabetes made a surprising discovery. Stephan Schilling was investigating how a pancreatic hormone resists degradation in the bloodstream.

1906 Alois Alzheimer, a German psychiatrist and neuropathologist, first describes “a peculiar disease” in the case of Auguste D., a patient who had profound memory loss, unfounded suspicions about her family, and other worsening psychological changes. In her brain at autopsy, he saw dramatic shrinkage and abnormal deposits in and around nerve cells.



Sources: Tangle visualization: P. Liu et al., *Signal Transduction and Targeted Therapy* 4, 29 (2019); Robert Katzman: S. Pincock, *The Lancet* 372, 1804 (2008) (opposite page)

He found that the hormone was chemically altered by an enzyme that adds pyroglutamate and that the same enzyme can add pyroglutamate to many other proteins—including amyloid beta.

During his postdoc, Schilling reported in 2008 that inhibiting this enzyme, called glutaminy l cyclase, curbs amyloid buildup and improves cognition in mice and fruit flies that model Alzheimer’s disease.

An inhibitor of the enzyme has been developed by Vivoryon Therapeutics AG, a German precision medicine company, and is now being tested in a study of people with mild Alzheimer’s disease, says Schilling, who is now a professor at Anhalt University of Applied Sciences and serves on Vivoryon’s scientific advisory board.

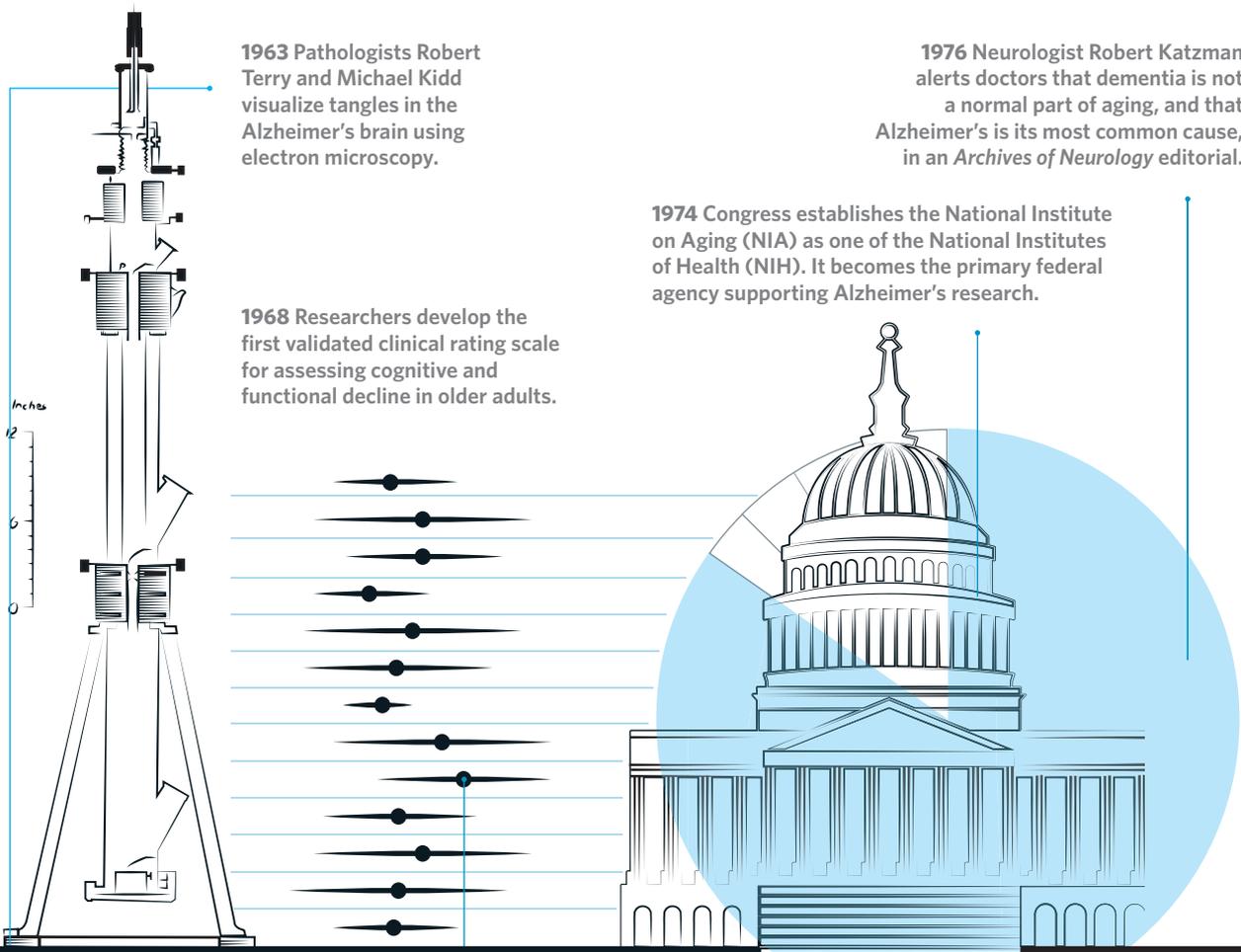
While developing the enzyme inhibitor, company researchers started pursuing another strategy—immunizing mice with antibodies against pyroglu Aβ. The rationale was that if pyroglu Aβ is found in

plaques, then targeting it with antibodies could lower brain amyloid and slow cognitive decline. Schilling and Lemere joined forces in 2008, testing pyroglu Aβ antibodies made by Probiodrug AG, which later became Vivoryon, on Lemere’s brain tissue samples and Alzheimer’s mouse models.

Amyloid immunotherapy

By then, amyloid had emerged as a prime focus for Alzheimer’s drug development. The first strategy to reach clinical testing was active immunotherapy: vaccinate with amyloid beta peptide to stimulate an immune response to remove amyloid deposits.

This approach worked in mice and was further studied in people with mild to moderate Alzheimer’s disease. But investigators stopped that trial in 2001 after 6 percent of participants developed brain inflammation, presumably resulting from an autoimmune response to injection with a naturally occurring protein.



1963 Pathologists Robert Terry and Michael Kidd visualize tangles in the Alzheimer’s brain using electron microscopy.

1968 Researchers develop the first validated clinical rating scale for assessing cognitive and functional decline in older adults.

1974 Congress establishes the National Institute on Aging (NIA) as one of the National Institutes of Health (NIH). It becomes the primary federal agency supporting Alzheimer’s research.

1976 Neurologist Robert Katzman alerts doctors that dementia is not a normal part of aging, and that Alzheimer’s is its most common cause, in an *Archives of Neurology* editorial.

First clinical rating scale: S. Tomaszewski Farias, *Neuropsychology* 22, 531 (2008)

Alzheimer's Impact on the Brain

The latest neuroscience tracks where the disease begins and how it progresses.

Alzheimer's disease impairs a patient by destroying neurons, which otherwise live for decades, and by disrupting communication among the remaining brain cells. As neurons die, the areas of the brain they constitute begin to atrophy. A detailed picture of the progression is still under investigation, and the disease follows different tracks in different patients, but researchers have found brains afflicted with Alzheimer's typically atrophy along the same basic pattern. A better understanding of that pattern may provide the foundation for methods to diagnose the disease earlier, which in turn would give medication and lifestyle changes the best chance of slowing dementia. In broad strokes, here's how Alzheimer's tends to change a brain. —KP

Regions of the Brain Most Affected

Cerebral cortex

Made of gray matter and located in the outermost layer of the brain, this wrinkled tissue contains more than 10 billion neurons and is responsible for advanced thinking and processing. It's divided into four major areas, which occur in pairs across the left and right hemispheres. Each region has a distinct specialty in mental functioning, and each has a distinct vulnerability to Alzheimer's.

Occipital Lobes **A**

Function: The occipital lobes mainly process input from the eyes. They recognize colors and shapes, integrate depth perception, and pass the resulting images on to the rest of the brain.

With Alzheimer's: Confusion, vision loss, and even hallucinations can happen as the area deteriorates, but the occipital lobes are affected relatively late in the typical progression of the disease.

Temporal Lobes **B**

Function: Conscious memories are stored in the temporal lobes. That includes both events in a person's past and general knowledge such as facts, meanings of words, and concepts.

With Alzheimer's: Atrophy in the temporal lobes happens early in Alzheimer's progression, which is why memory loss is often an early symptom. In late-stage Alzheimer's, temporal lobes can shrink considerably.

Parietal Lobes **C**

Function: The parietal lobes compile sensory inputs to deduce the body's position in space and allow a person to recognize environments. The region is also responsible for reading and writing.

With Alzheimer's: Parietal lobes experience significant atrophy, which can create difficulty with reading and writing. It also disrupts telling left from right; identifying objects by touch; and getting dressed and performing other complex spatial tasks.



The Progression of Alzheimer's Disease

The clinical hallmarks of Alzheimer's include the proteins amyloid beta and tau, as well as neurological degeneration as neurons die. Here's the typical progression in time.



healthy brain



early degeneration

1. Preclinical

Before memory loss begins, the brain, bloodstream and cerebrospinal fluid begin to accumulate amyloid beta and tau. The buildup happens either because the brain (shown here in a front cutaway view) is making too much of the proteins or because the body isn't clearing them fast enough. Alzheimer's begins after neurons start dying, with degeneration visible on a brain scan.



Frontal Lobes **D**

Function: Decision-making, impulse control, and other more advanced cerebral tasks happen in the frontal lobes.

With Alzheimer's: Frontal lobes atrophy relatively late in the disease, but when they do, attention, task-switching, and appropriate social behavior are all affected.

Subcortical structures

A collection of smaller components that collectively make up about 25 percent of the brain's volume, the subcortical structures are involved in both higher and lower thinking. Collectively, they act as an information hub for the brain while also governing emotional regulation, motivation and movement control.

Amygdala

Function: Emotional processing happens in this almond-shaped structure, nestled between the hippocampus and the frontal lobes. It activates fear responses and links memories with emotion.

With Alzheimer's: The amygdala begins to atrophy early in the progression of Alzheimer's. The effects of that atrophy are still being studied, but there's evidence that it leads to agitation and aggression.

Thalamus

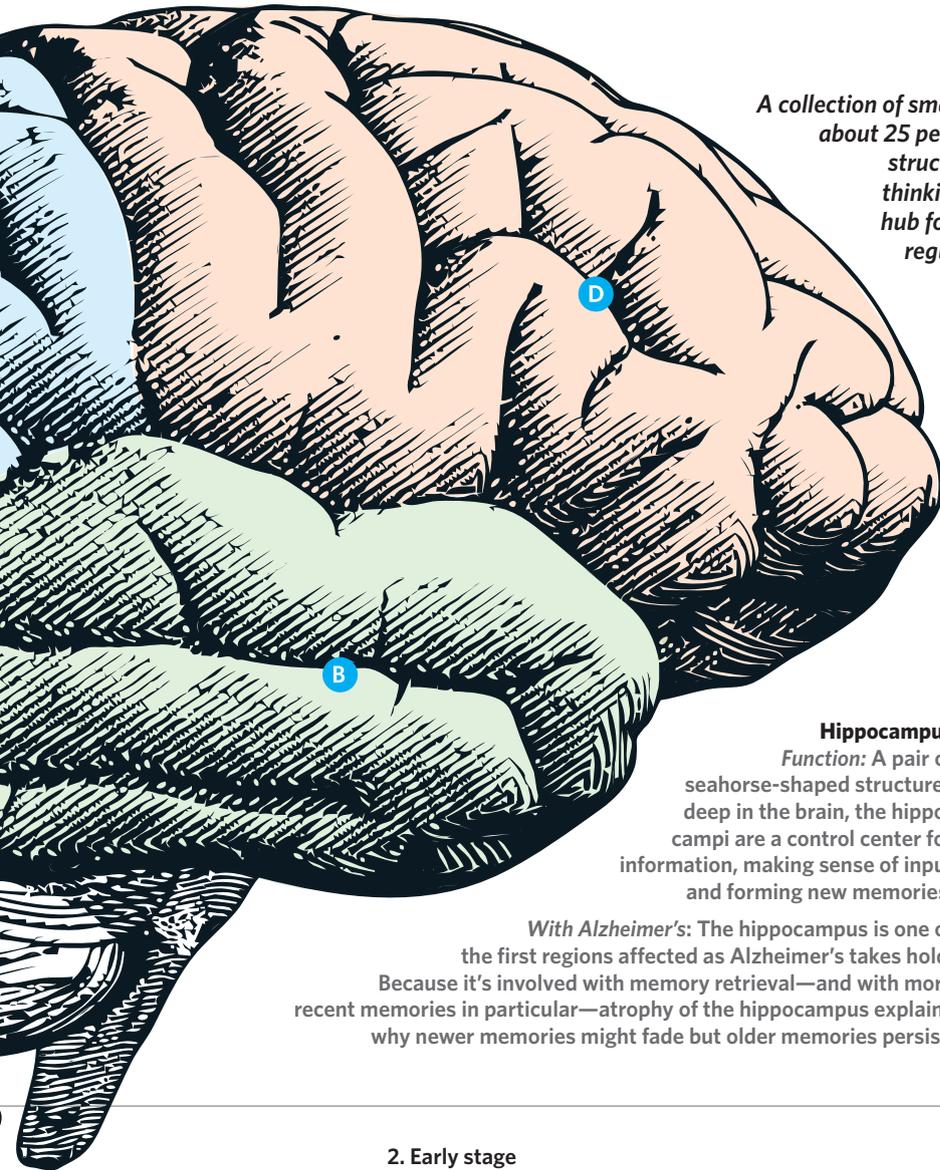
Function: Shaped like a small egg, the thalamus is a critical hub for information in the brain. It relays sensory inputs to the higher-level gray matter (the cerebral cortex), while also governing wakefulness and attention.

With Alzheimer's: Imaging and post-mortem studies of patients with advanced Alzheimer's tend to show atrophy in this region.

Hippocampus

Function: A pair of seahorse-shaped structures deep in the brain, the hippocampi are a control center for information, making sense of input and forming new memories.

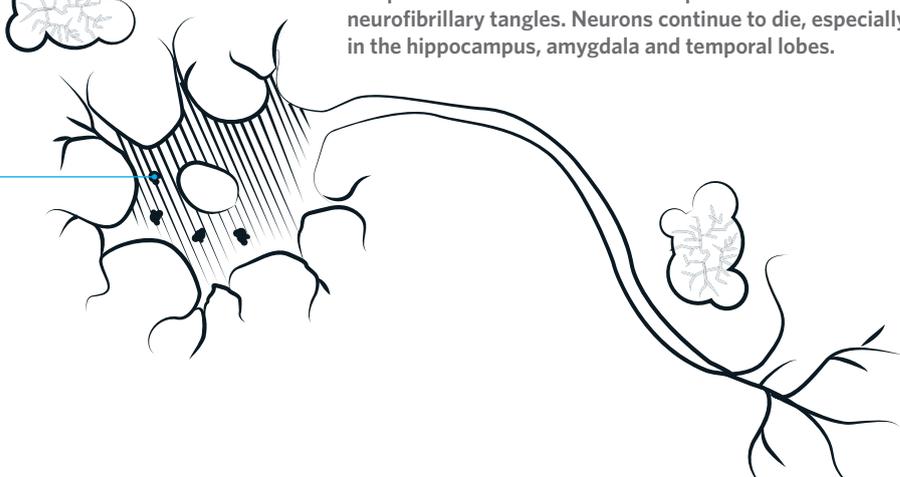
With Alzheimer's: The hippocampus is one of the first regions affected as Alzheimer's takes hold. Because it's involved with memory retrieval—and with more recent memories in particular—atrophy of the hippocampus explains why newer memories might fade but older memories persist.



2. Early stage

As the disease progresses, amyloid beta begins to form plaques in the brain areas between the neurons. Tau proteins within neurons build up into so-called neurofibrillary tangles. Neurons continue to die, especially in the hippocampus, amygdala and temporal lobes.

—amyloid plaque



3. Late stage

After years or even decades, a brain with Alzheimer's will have significant amyloid plaque buildup and visible atrophy in other brain regions, including the parietal lobes.



To avoid those harmful effects, some Alzheimer's trials turned to passive immunotherapy—injecting antibodies directly into the patient rather than stimulating the patient's body to make them.

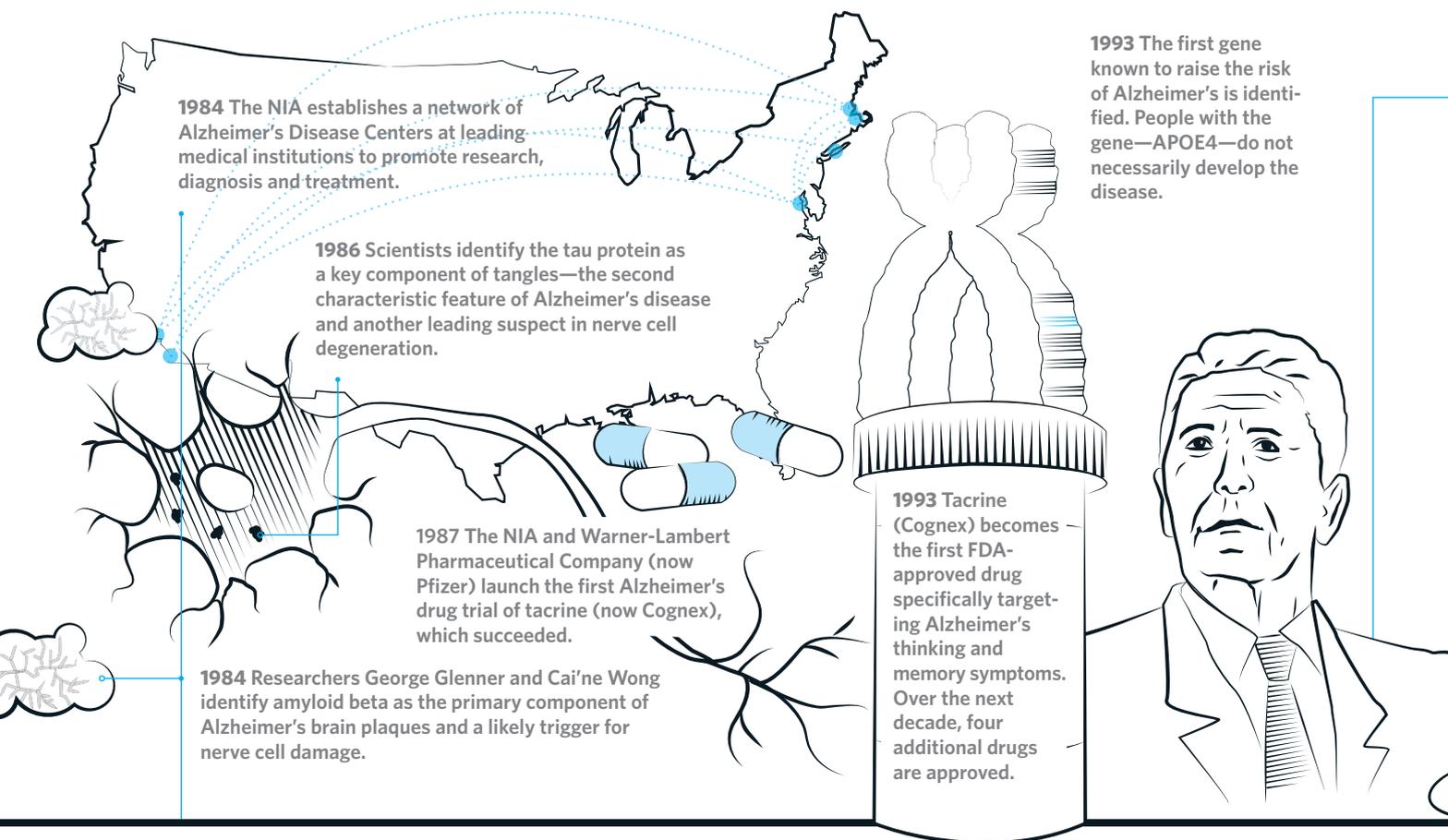
Scientists at Lilly Research Laboratories in Indianapolis developed an antibody that binds soluble amyloid beta, thinking this could shift the equilibrium to prevent neurotoxic aggregates from forming. The antibody looked impressive in Alzheimer's mice, reversing memory deficits even as amyloid piled up in their brains. But when Eli Lilly created a humanized version of this antibody and moved it into clinical trials, the antibody, solanezumab, failed to help patients with mild to moderate symptoms who enrolled in two late-stage, placebo-controlled studies. Meanwhile, bapineuzumab, an antibody that recognizes both soluble and plaque amyloid, also

failed in a large phase 3 trial; Johnson & Johnson and Pfizer decided in 2012 to discontinue this drug.

Although the drugs failed to help patients, the two studies did mark the first use in Alzheimer's research of an important new tool: positron emission tomography (PET) brain scans that measure amyloid load in the brains of live patients. PET revealed that nearly a quarter of participants in the solanezumab and bapineuzumab trials did not in fact have Alzheimer's—their scans showed no brain amyloid—so the tested drugs could not have helped them. And though the Alzheimer's antibody trials were failing to identify new drugs, collectively the trials were teaching researchers something valuable: experimental treatments seem to work better when started earlier in the disease process.

Soon Eli Lilly took another shot: It enrolled 2,129 patients in an 18-month trial, in which they would

“It’s important to try to find ways to mitigate ARIA. Before I retire, I have to figure this out.”



receive monthly infusions of either the drug solanezumab or a placebo. To qualify for that study, participants had to test positive for amyloid, by brain scan or spinal fluid analysis. Yet even with the tightened criteria, the company reported in late 2016 that treated patients showed only a hint of improvement, relative to the placebo group. “It did move the needle, but not enough to be a medicine,” says Eric Siemers, who started a consulting business in 2017 after 19 years directing Eli Lilly’s Alzheimer’s disease program. “That was a big disappointment.”

And although passive immunotherapy has proved safer by avoiding the brain inflammation that halted the 2001 active immunotherapy trial, antibody infusions still raise concern. A subset of participants develop brain swelling and microbleeds—amyloid-related imaging abnormalities (ARIA), which show up on magnetic resonance imaging (MRI) scans. Some patients experience symptoms—typically headache, confusion or nausea—and three participants in clinical trials with ARIA have died, so patients with ARIA symptoms must

be monitored. But most ARIA cases are asymptomatic, transient and resolve with corticosteroids.

Despair and determination

Alzheimer’s drug development is high stakes and high risk. More than 300 interventions—79 of them amyloid-related—have entered clinical testing, and 99 percent of experimental therapies have performed no better than placebo in clinical trials, according to the therapeutics database at Alzforum, a web resource for researchers studying Alzheimer’s and related disorders.

Given these tough odds, companies hedge their bets. While testing antibodies, some also pursued other amyloid strategies—for example, a pill that reduces amyloid beta levels by blocking the activity of an enzyme called BACE1 that is required to produce it. “A lot of people were convinced that these BACE inhibitors were going to be the solution,” Siemers says.

But four large studies of such drugs showed no drug-placebo difference in Alzheimer’s patients; in

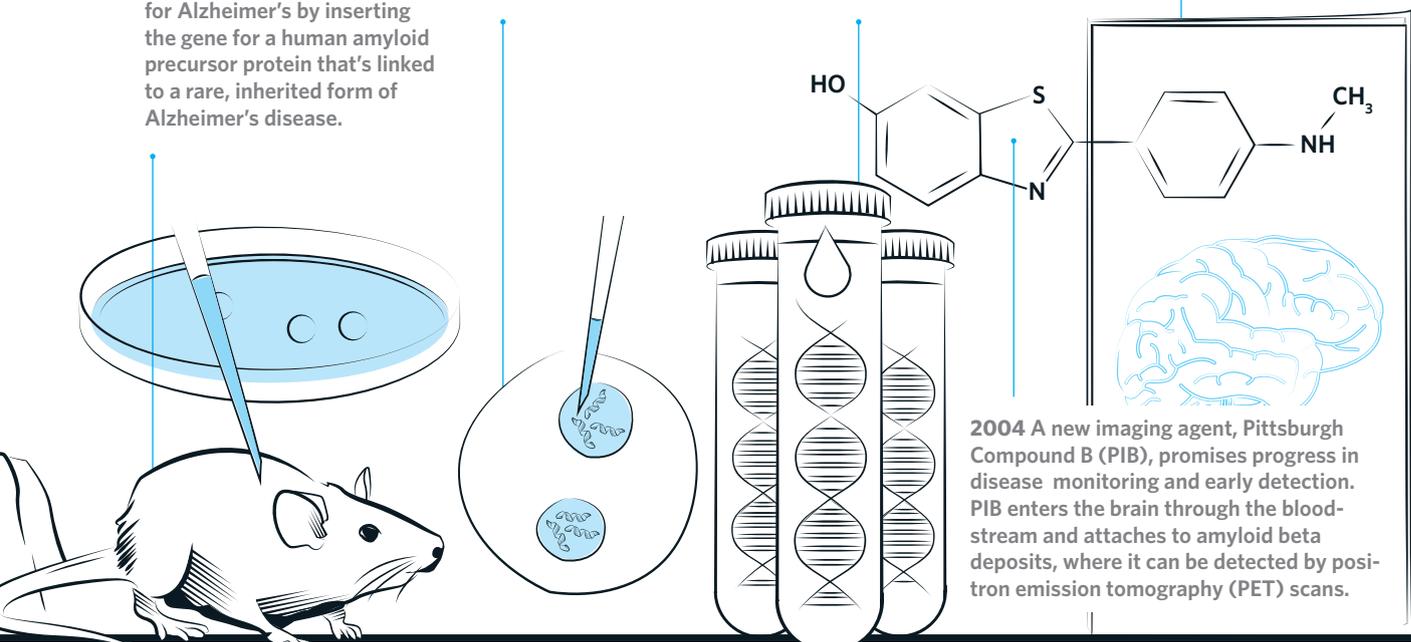
1994 Former U.S. President Ronald Reagan shares that he has been diagnosed with Alzheimer’s disease.

1995 Scientists develop the first transgenic mouse model for Alzheimer’s by inserting the gene for a human amyloid precursor protein that’s linked to a rare, inherited form of Alzheimer’s disease.

1999 The first “Alzheimer’s vaccine”—injections of amyloid beta—prevents transgenic “Alzheimer mice” from developing plaques and other brain changes typical of the disease.

2003 To identify additional Alzheimer’s risk genes, the NIA launches the National Alzheimer’s Disease Genetics Study to collect blood samples from families prone to late-onset Alzheimer’s.

2005 The Healthy Brain Initiative is launched by the CDC and the Alzheimer’s Association with the publication of A National Public Health Road Map to Maintaining Cognitive Health.



2004 A new imaging agent, Pittsburgh Compound B (PIB), promises progress in disease monitoring and early detection. PIB enters the brain through the bloodstream and attaches to amyloid beta deposits, where it can be detected by positron emission tomography (PET) scans.

fact, treated participants actually got a bit worse. For some researchers, the failed trial of Merck's BACE inhibitor in 2019 was a breaking point. It prompted a reevaluation in the field. "To be blunt, amyloid-beta lowering seems to be an ineffective approach, and it is time to focus on other targets to move therapeutics for Alzheimer's disease forward," Mayo Clinic neurologist David Knopman wrote in a 2019 commentary shortly after the failed trial.

For Schilling, such declarations instilled determination to continue the research. "I wanted to show all these people that [pyroglu A β] is a concept that is viable and that can be used to develop a treatment," he says. Meanwhile, Lemere's team used the pyroglu A β antibody developed by Schilling's Probiodrug colleagues to treat Alzheimer's in mice. Reporting in a February 2012 paper, "we found that we were clearing regular amyloid beta as well," she says.

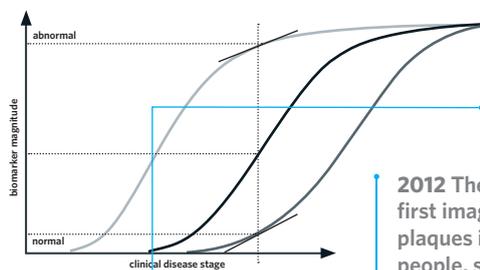
A team from Eli Lilly published similar findings with their pyroglu A β antibody later that year and ultimately advanced it into clinical testing before the smaller Probiodrug team could. In spring 2021, the company reported that this drug, donanemab, slowed cognitive decline in a phase 2 trial of 257 participants with early Alzheimer's disease.

New hope

That was a "turning point," says Knopman, whose enthusiasm for amyloid-lowering treatments had waned with past failures of BACE inhibitors and immunotherapy trials. More success followed. In 2022 Eisai and Biogen reported that participants with early-stage Alzheimer's who were treated with another amyloid antibody, lecanemab (Leqembi), declined 27 percent more slowly than the placebo group in a large 18-month trial. And in summer 2023, Eli Lilly reported that donanemab slowed cognitive worsening by 35 percent in amyloid-positive mild Alzheimer's patients who also had low to moderate levels of another protein, tau.

The latest results suggest that patients lose function five months later than they would have otherwise during 18 months of treatment, according to a recent analysis by researchers at Pentara, a clinical trials consulting firm. This could preserve their ability to drive or delay their need to move into a nursing home, says CEO Suzanne Hendrix, a statistician who helped Eisai design a key scoring metric for the pivotal trial leading to lecanemab's FDA approval.

As the newest Alzheimer's drugs begin the challenging transition from research trials to real-world use, researchers are testing new types of therapies



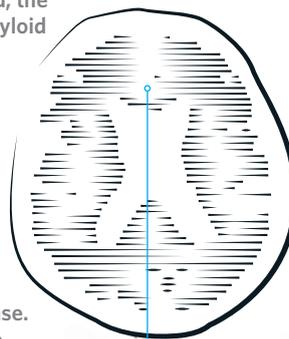
2010 Researchers publish a working model relating changes in Alzheimer's biomarkers to disease stage and symptom severity. The model has since become a focal point of research into Alzheimer's biomarkers, and is revised periodically to account for new research.

2010 Data released by the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics show that Alzheimer's disease has become the sixth leading cause of death in the U.S.

2012 The FDA approves Amyvid, the first imaging agent to reveal amyloid plaques in brain scans of living people, suggesting that PET scans can be used to diagnose the disease.

2012 Researchers from Iceland report first gene mutation that protects against Alzheimer's. Icelanders with this mutation are five times as likely to reach 85 without developing the disease. The work points to amyloid beta as a therapeutic target.

2013 The largest-ever Alzheimer's gene study, the International Genomics of Alzheimer's Project identified 11 new genetic variations that increase the risk of Alzheimer's disease, including some that seem to confirm the immune system's key role in the disease.



“If my amyloid beta and tau are high, maybe I get on a drug that can lower those and prevent me from getting Alzheimer’s, and in someone else it might be a different brain protein. These panels are going to tell us what is going on in the brain and what we might be at risk for developing over time.”

that they hope can achieve stronger benefits with fewer side effects.

Eli Lilly itself is working on a newer pyroglutamate antibody that eases some of donanemab’s side effects and seems to clear plaques faster, according to early data reported this spring. And researchers at Vivoryon, working with Schilling and Lemere, are trying to re-engineer their pyroglu Aβ antibody so it cannot activate the immune reactions underlying ARIA.

“It’s important to try to find ways to mitigate ARIA,” says Lemere. “Before I retire, I have to figure this out.”

Meanwhile, several companies are still pursuing active immunotherapy by creating safer amyloid beta vaccines that could one day be deployed to prevent disease, especially once blood tests replace the much costlier brain scans to detect preclinical Alzheimer’s.

In another decade or so, some researchers think such blood panels could become routine—and they would check not just amyloid and tau but also other proteins that are associated with dementia or neurodegeneration. Screening would start around age 65 or 70. “If my amyloid beta and tau are high, maybe I get on a drug that can lower those and prevent me from getting Alzheimer’s, and in someone else it might be a different brain protein,” says neurologist Gil Rabinovici, who directs the Alzheimer’s Disease Research Center at the University of California, San Francisco. “These panels are going to tell us what is going on in the brain and what we might be at risk for developing over time.”

Esther Landhuis is a science journalist who has written for Nature, Medscape, Undark, Quanta, Science News, NPR and others. She holds a Ph.D in immunology from Harvard University.

2014 “I’ll Be Me,” a documentary by James Keach, follows country singer Glen Campbell on his last tour as he struggles with Alzheimer’s. By opening up about the disease, Campbell and his family began to ease its stigma.

2019 Annual NIH funding for Alzheimer’s and dementia research in the U.S. receives a \$350 million increase and reaches \$2.8 billion, an all-time high.

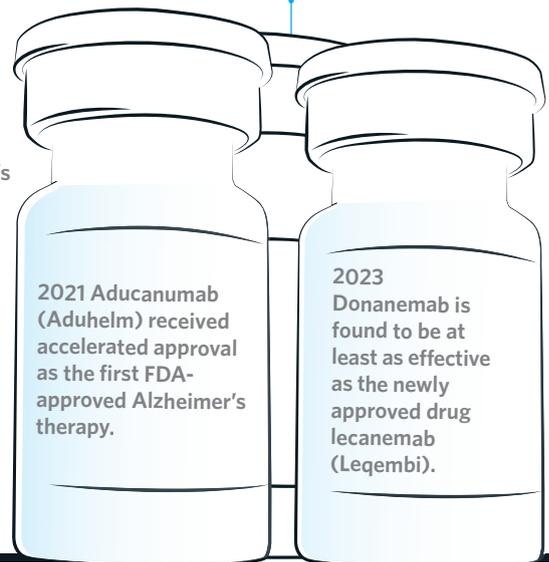
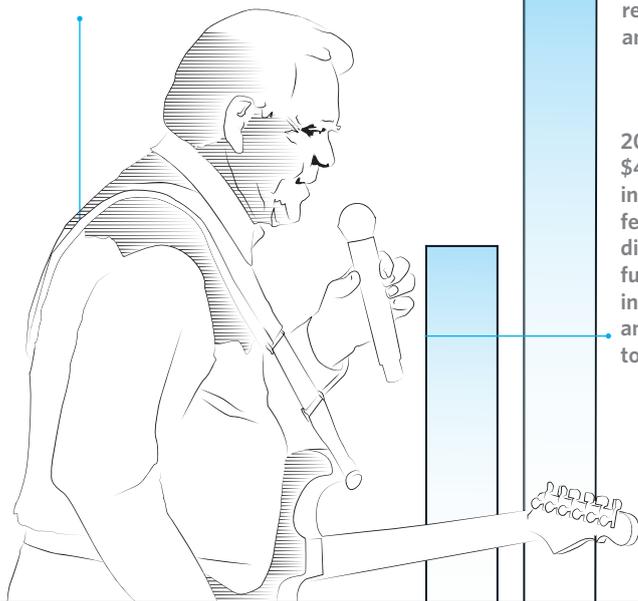
2023 Lecanemab (Leqembi) receives FDA approval for the treatment of early Alzheimer’s disease with confirmation of elevated amyloid beta. This is the first traditional approval of an Alzheimer’s treatment that changes the underlying course of the disease.

2017 A historic \$400 million increase in U.S. federal Alzheimer’s disease research funding is signed into law, bringing annual allotment to \$1.4 billion.

2021 Aducanumab (Aduhelm) received accelerated approval as the first FDA-approved Alzheimer’s therapy.

2023 Donanemab is found to be at least as effective as the newly approved drug lecanemab (Leqembi).

IMAGES: ALZHEIMER’S BIOMARKERS: C. JACK ET AL., THE LANCET NEUROLOGY, 9, 119 (2010); LARGEST ALZHEIMER’S GENE STUDY: J.-C. LAMBERT ET AL., NATURE GENETICS, 45, 1452 (2013). (PRECEDING PAGE)



Donanemab effectiveness: “The Alzheimer’s Treatment Landscape: Leqembi vs. Donanemab,” by Heather McKenzie, BioSpace, September 2023.



An Alzheimer's Test for Everyone

In just a few years, annual checkups may include a blood test that screens for Alzheimer's, ushering in a new era of preventive medicine.

BY SUZANNE SCHINDLER | ILLUSTRATION BY HAROL BUSTOS

Henry, a carpenter in his late 50s who worked for a small business, had been making and refinishing furniture for years. Then he started having difficulty using tools. The quality of his work rapidly declined, and eventually he was fired. At home, his wife grew frustrated with him for forgetting their conversations. He was not doing a good job with chores such as loading and unloading the dishwasher.

Henry went to see a doctor, who referred him for cognitive testing. The results came back “invalid.” Among the potential diagnoses the neuropsychologist came up with was “malingering”—basically faking his cognitive impairment. The specialist apparently did not anticipate that someone so young might have dementia. As a result, Henry’s application for disability benefits was denied.

By the time Henry walked into my clinic at Washington University in St. Louis, he and his family were confused and desperate. His wife thought perhaps Henry was being lazy and didn’t want to work or help around the house. But he seemed to struggle with simple tasks, such as dressing himself, and his problems were getting worse. She was worried.

As a cognitive neurologist, many patients come to see me because they’ve noticed subtle changes in their memory and thinking. Their major question is, “Do my symptoms represent the beginning of a progressive neurological illness like Alzheimer’s disease?” The answer is often not clear at their first visit, even after I take a detailed history, do brain imaging, and check routine blood work. Mild problems with memory and thinking are relatively common and can have many causes, such as poor sleep,

stress, sleep apnea, various medical conditions, and certain medications.

When patients with subtle changes in memory and thinking come to our clinic and the cause is unclear, a common strategy has been “cognitive monitoring”—watching patients over time to see if their problems get better, stay the same, or get worse. Some patients improve after interventions such as stopping a medication or starting treatment for sleep apnea. Some patients continue to experience cognitive difficulties but never really worsen. And some patients progressively decline until it becomes clear that they have a neurological disorder. Which leads to another difficult question: Are their symptoms caused by Alzheimer’s disease?

Clinicians define dementia as a decline in memory and thinking that affects a patient’s function in everyday activities. There is a continuum of dementia, from being unnoticeable by people who do not know the patient well to causing complete dependence on others for dressing, bathing, eating, toileting and other simple tasks. Dementia, particularly when very mild, can have many causes, some of which are treatable. Alzheimer’s is the most common cause of dementia in patients older than 65 years. It is characterized by specific brain changes, including the deposition of amyloid plaques. These brain changes slowly worsen over time and can be detected 10 to 20 years before the onset of symptoms.

Not long ago, it was impossible to know for sure whether a patient with cognitive impairment had Alzheimer’s disease or some other cause of dementia without an autopsy. In recent years we have vastly improved our diagnostic capabilities. We can now offer blood tests that can enable earlier and more accurate diagnoses of large numbers of people.

Given the need for rapid diagnosis of Alzheimer’s, I expect that blood tests will become the dominant approach to testing.

Spinal taps and amyloid PET scans

In 2012, the U.S. Food and Drug Administration approved amyloid PET scans, which can reveal the presence of the amyloid plaques characteristic of Alzheimer's disease and which are thought to initiate a cascade of brain changes that culminate in dementia. In 2022, the FDA approved the first test for Alzheimer's disease that measured amyloid proteins in the cerebrospinal fluid or CSF.

For more than a decade, neurologists like me had been using CSF tests to determine whether patients with cognitive impairment were likely to have Alzheimer's brain changes. While neurologists perform spinal taps to collect CSF to test for a variety of conditions, and it is safe and well-tolerated, most people have never had a spinal tap and it may seem scary. Even if the CSF testing provides a more certain diagnosis, patients often aren't interested in having a spinal tap unless it has a major impact on their care. Patients will ask, "If I test positive, is there anything you would do differently?" For years, in most cases I have said, "Probably not," and that I would still treat them with the same medications and follow them in the same way. For this reason, we didn't do many tests for Alzheimer's—as my patients put it, "There's nothing we can do about it anyway."

There were some exceptions. I did CSF testing on Henry, the carpenter who could no longer build furniture or load the dishwasher. It was positive for Alzheimer's disease. As I had suspected, Henry had an atypical form of Alzheimer's that affects brain circuits involved in visual-spatial functioning—exactly the ones Henry needed in his work. With a clear diagnosis, Henry was able to get disability benefits, and his wife understood that his issues were caused by a brain disease.

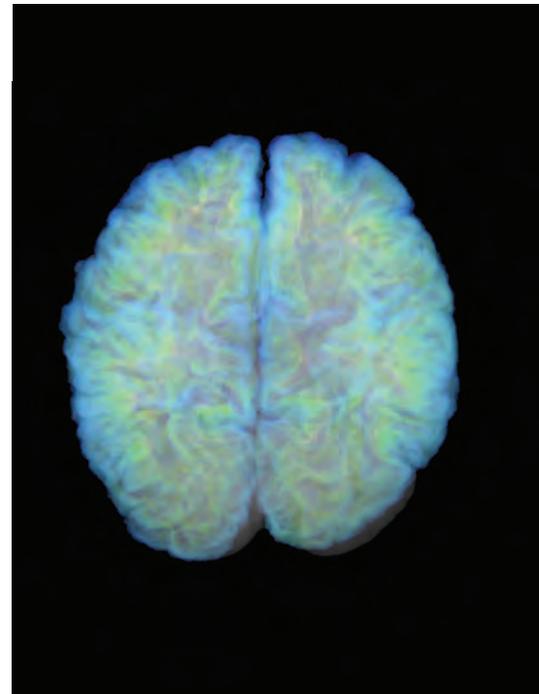
Amyloid PET scans are another technique that can be used to detect and quantify the amyloid plaques characteristic of Alzheimer's. The patient is injected with a very small amount of a radioactive tracer that binds amyloid plaques in the brain. Positron emission tomography (PET) is a sophisticated imaging technique that can take pictures of this radioactivity and visualize the distribution of amyloid plaques in the brain. An amyloid PET scan, however, costs around \$6,000 in my medical system. There are also not that many PET scanners. The largest study of amyloid PET, called the IDEAS study, performed 20,000 scans over about 18 months in sites all over the U.S. That's a lot of scans, but the number of people who might need testing for Alzheimer's could be in the hundreds of thousands or even millions.

The era of Alzheimer's treatments

On July 6, 2023, a treatment for Alzheimer's disease that attacks an underlying cause of disease was fully approved by the FDA. This treatment, lecanemab, works by clearing amyloid plaques from the brain of patients with mild symptoms of Alzheimer's and slows the progressive cognitive decline. A similar treatment, donanemab, has done well in clinical trials. While we need even better treatments, we are finally starting to make progress against Alzheimer's. And there are now nearly 150 treatments being studied in clinical trials.

Now that there are specific treatments, testing for Alzheimer's needs to be done in many more patients, not just the occasional patient like Henry. These treatments are likely to be most effective if given to patients early in the disease, when symptoms are mild. Cognitive monitoring for a year or two isn't reasonable now that there may be "something we can do

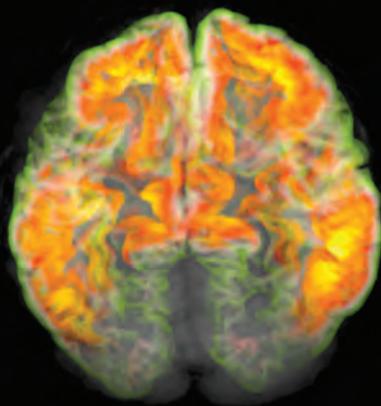
Positron emission tomography (PET) imaging can now detect the presence of amyloid plaque in the brain, a sign of Alzheimer's disease. The brain on the right has plaque, while the one on the left does not.



about it". However, relatively few patients with mild cognitive concerns visit a neurologist and undergo a comprehensive dementia evaluation that includes amyloid PET and CSF testing, and many patients are not diagnosed with Alzheimer's dementia until the disease has progressed beyond the point that new treatments may be helpful. Now that a treatment is available that is most effective early in the disease, there is a sense of urgency to the diagnosis of Alzheimer's disease.

About three years ago, our memory clinic performed about five spinal taps a month. Now that lecanemab is available, we have scaled up and are now performing about 30 spinal taps per month. It's difficult to do many more, because the procedure is very time-consuming. We spend about 10 to 15 minutes talking about the procedure and getting consent, which is necessary because most patients have never had a spinal tap and some are anxious about it.

Blood biomarker tests may supplant CSF and amyloid PET testing, for individuals who suspect they may have Alzheimer's disease, within the next three years.



The procedure takes about 20 minutes. Afterwards a small number of patients have issues such as back pain or headache, which may require additional follow-up. Amyloid PET scans can be costly, even when insurance covers them, so we haven't been ordering them very often. Both amyloid PET and CSF tests are highly accurate for detecting the brain changes of Alzheimer's, but they are too expensive and cumbersome to be used for every person suspected of having Alzheimer's.

Blood tests for Alzheimer's

Blood tests are the critical tool needed to enable large-scale testing that may allow for more rapid diagnosis of Alzheimer's and initiation of treatments when they are most effective. Unlike CSF testing and amyloid PET scans, blood tests are already a routine part of healthcare. When I see a patient with memory and thinking problems, I send them for routine blood work that includes blood counts, blood chemistries, a vitamin B-12 level, and thyroid function studies. However, in patients coming to see me because of cognitive concerns, these routine studies are much less informative than an Alzheimer's blood test would be.

Since 2017, researchers have made remarkably rapid progress in developing blood tests for Alzheimer's. Some of these blood tests are now available in the clinic, and many more are on the way. The tests generally measure a handful of different proteins that are strongly associated with Alzheimer's brain changes. Levels of these proteins can help clinicians decide whether a patient's cognitive symptoms are likely to be caused by Alzheimer's. Blood tests are also now being used by clinical trials to identify older, cognitively normal individuals with early Alzheimer's brain changes who are at high risk of developing dementia.

The first blood test for Alzheimer's was developed in the laboratory of Randall Bateman at Washington University and became available for clinical use in December 2020. It measured the ratio of two forms of amyloid in the blood and determined a person's forms of apolipoprotein E, which is a major risk factor for Alzheimer's. More recently, Nicolas Barthelemy, working in Bateman's laboratory, developed an even better test that measures specific tau proteins in the blood. A version of this tau blood test combined with the amyloid test is now being used in our clinic for select patients. Although studies are still underway and the test is not yet FDA-approved, initial results suggest that this tau blood test has similar or even higher accuracy than CSF tests.

Recognizing that blood tests for Alzheimer's are critically needed, many other researchers and companies have been working to develop their own. There are now at least 16 Alzheimer's blood tests in various stages of development. Some tests, like Barthelemy's, are highly accurate while other tests perform quite poorly. Somewhat surprisingly, the requirements to market a test to patients are low, leading to the avail-

ability of Alzheimer's tests in the clinic that are not well validated and would result in the misdiagnosis of many patients.

How accurate does an Alzheimer's blood test need to be? Even amyloid PET and CSF tests, while strongly associated with Alzheimer's brain changes, aren't perfect. Is it acceptable to misdiagnose one in four patients? (I certainly don't think so.) Is it acceptable to misdiagnose one in 10 patients, or one in 20? Does it make a difference if the misdiagnosed patient is actually on the borderline of having early Alzheimer's brain changes?

After returning the results of Alzheimer's tests to many patients over the past decade, my conclusion is that tests used in clinical diagnosis need to be highly accurate. A diagnosis of Alzheimer's disease changes the way patients see themselves and their future; the information guiding this diagnosis must be correct. Accuracy is especially important if patients are going to be started on an Alzheimer's-disease-specific treatment based on this test result.

After much discussion with colleagues, we generally agree that blood tests used in clinical diagnosis need to be on par with FDA-approved CSF tests or we probably would not use them and ideally would correctly classify 90 to 95 percent of patients. Some of the newest blood tests meet this high threshold, especially because they can categorize individuals as positive, negative, and intermediate. Identifying individuals in this intermediate category, who have borderline levels of Alzheimer's brain changes, allows much greater confidence in the positive and negative results. Individuals with intermediate results can be re-tested in a year or assessed with another type of test.

Given the greatly increased need for more rapid diagnosis of Alzheimer's, and the major limitations of spinal taps and amyloid PET, I expect that blood tests will become the dominant approach to testing for Alzheimer's disease brain changes within a few years. Because blood collection is so accessible, use of Alzheimer's blood tests would enable us to test most patients presenting for cognitive concerns, rather

than the occasional patient like Henry. Broad-based blood testing is the only way that we will be able to identify most individuals with very early symptoms of the disease. Although these Alzheimer's blood tests are currently used almost exclusively by cognitive neurologists like me, as the tests are better validated and clinicians learn more about them, they

will certainly enter into primary care settings. This is largely because there are so many older adults and so few cognitive neurologists.

In another couple of years, there may be another transformation. Clinical trials are now underway to test whether certain treatments, when used in cognitively normal individuals with Alzheimer's brain changes, can prevent or slow the onset of dementia. If those trials are successful and demonstrate that we can stave off Alzheimer's dementia, we could enter a time where primary care

clinicians screen cognitively normal older individuals at annual visits with blood tests to see whether they have Alzheimer's brain changes. This may herald an era when Alzheimer's disease becomes a chronic medical management issue, like high cholesterol, rather than the devastating illness that we know today.

There is a clear public-health benefit for making blood biomarker tests as accurate as possible—so that fewer people would have to be referred for additional, expensive testing.

Suzanne Schindler is a clinical neurologist and neuroscientist focused on improving the diagnosis and treatment of Alzheimer's disease. She completed the M.D./Ph.D. program and trained in neurology at Washington University. She currently sees patients with memory concerns and coordinates biomarker testing for the Washington University Memory Diagnostic Center. She leads the Fluid Biomarker Core for the Knight Alzheimer Disease Research Center.

Disclosures: Schindler served on a Scientific Advisory Board for Eisai. Washington University has an interest in C2N Diagnostics, a company that offers an Alzheimer's blood test. She does not have any financial interest in C2N Diagnostics or any other pharmaceutical or diagnostic companies. Some details about Henry, including his name, have been modified to protect his confidentiality.

How to Detect Alzheimer's Before Symptoms Appear

New technologies for catching the disease in the early stages are critical for slowing the progression of the disease—and perhaps one day forestalling it entirely.

The best time to treat Alzheimer's is early, but it's a stealthy thief. By the time symptoms of cognitive decline become apparent, the disease has been slowly and invisibly changing the brain for as much as 20 years. PET scans and tests of cerebrospinal fluid can reveal the biomarkers of this early activity, but to screen large populations, doctors need less expensive and less invasive methods. Scientists are now developing a range of technologies for early detection. No single test is expected to solve the problem—it will probably take a constellation of different screenings. "This is a complex disorder," says Mark Roithmayr, head of the Alzheimer's Drug Discovery Foundation. "Let's embrace the complexity and bring in a multifactorial approach." Here are some of the most promising ones. —KP



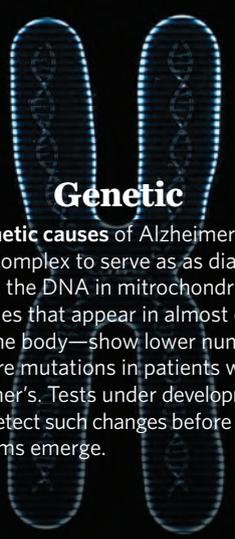
Blood-based

Alzheimer's is a disease of the nervous system, but it triggers complex changes in the body that sometimes turn up in the blood. Successful screenings may combine measurements of many different factors, such as levels of tau and amyloid beta, brain inflammation, and proteins, called neurofilaments, released when the brain begins to atrophy.



Ocular

A visit to the eye doctor may soon include a screening for Alzheimer's. Early stages of the disease cause changes in the brain that ripple out through the nervous system to the optic nerve. Scientists can now detect them with retina scans, and several firms are developing commercial technologies. (For more, see page 51.)



Genetic

The genetic causes of Alzheimer's may be too complex to serve as diagnostics. But the DNA in mitochondria—organelles that appear in almost every cell in the body—show lower numbers and more mutations in patients with Alzheimer's. Tests under development might detect such changes before clinical symptoms emerge.



Digital

Smartphones and fitness trackers have an intimate view of their owner's sleep patterns, cognition and motor function. A team at Boston University is developing an algorithm that detects dementia based on a 10-minute questionnaire, which anyone can take for free and which allows patients to track their results over time to look for signs of decline.

Early Dementia Symptoms

Important areas that testing strategies are targeting:

Memory loss, especially difficulty with recently learned information and asking the same question repeatedly

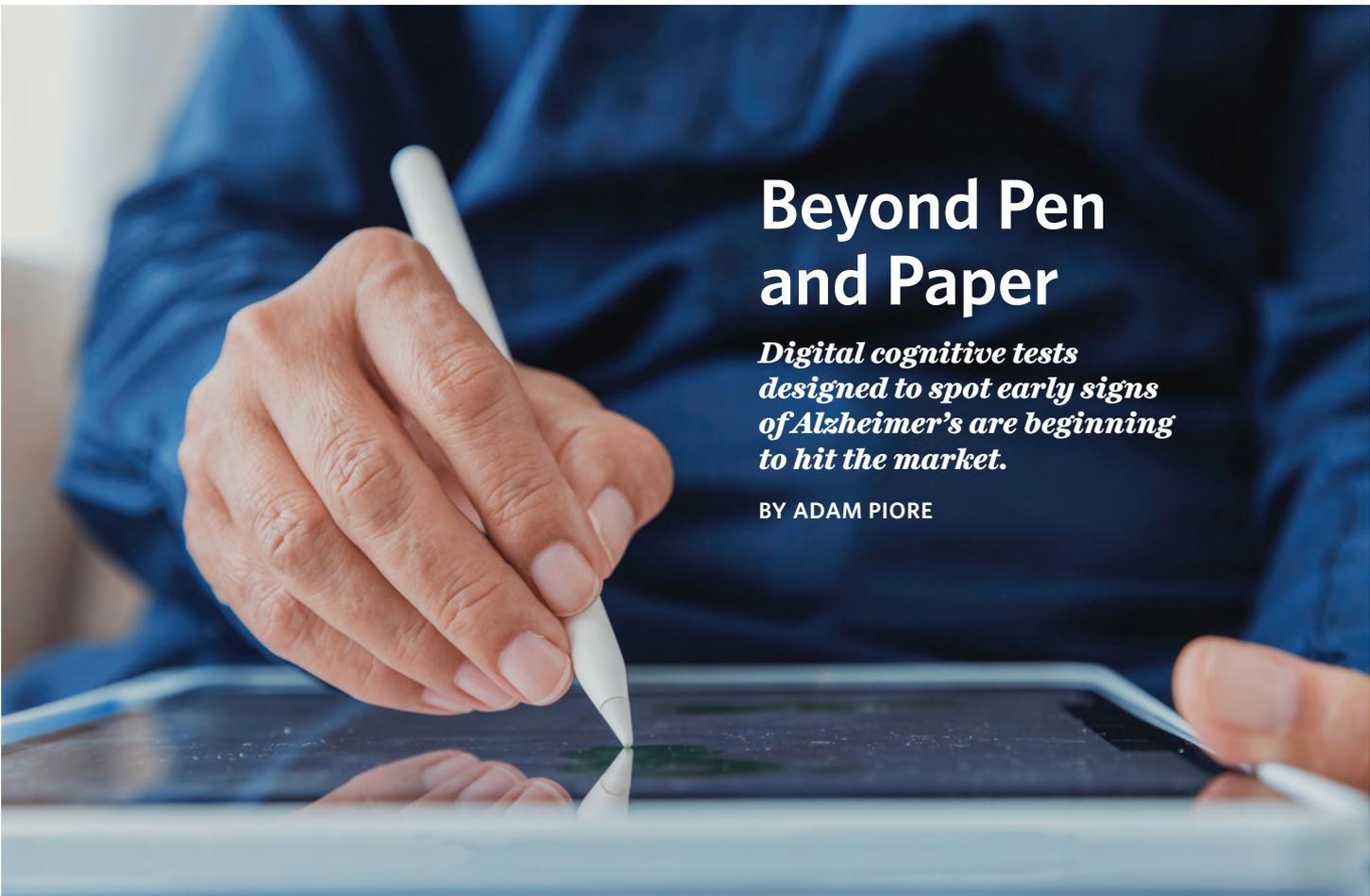
Concentration problems, such as difficulty following a recipe or making decisions

Language difficulty. For example: upon trying to recall a name, the person draws a blank—as opposed to remembering the first letter or number of syllables in a name, which is considered normal forgetfulness

Perception trouble, especially with recognizing objects, judging distances and interpreting patterns—for example, mistaking a friend's identity

Location and time confusion, for example, leaving on an errand and forgetting how to get home again

Mood shifts, including rising levels of anxiety, irritability and apathy



Beyond Pen and Paper

Digital cognitive tests designed to spot early signs of Alzheimer's are beginning to hit the market.

BY ADAM PIORE

Many primary care doctors have had a complicated relationship with tests designed to screen their patients for Alzheimer's disease. Beyond recommending a few lifestyle changes—tweaks to diet, exercise and sleep most would recommend anyway—there was little they could do to help patients with a confirmed diagnosis.

As new drugs expand the options for treating and preventing Alzheimer's, demand from older people worried about their mental fitness and seeking routine screening for Alzheimer's and other dementia is expected to rise quickly. In anticipation, several commercial firms are racing to bring to market new digital screening tools that can detect warning signs that the disease could be developing.

(Diagnostic tools, by contrast, are used to establish the presence of the disease, usually by detecting amyloid.) Many of these new screening tools use artificial-intelligence algorithms and can be administered by medical assistants without extensive training. They hold out the promise of inexpensive and noninvasive methods of screening people for Alzheimer's.

“Dementia is the number-one fear of people over 55,” says David Bates, CEO of Boston-based Linus Health, a digital assessment company. “You have drug companies that are about to be advertising their drugs. And you're going to have commercials and marketing stoking that fear to drive people to ask for the drug. So you're going to have this onslaught of demand in the health system. Primary care doctors will not be able to meet that demand. They're going to get overwhelmed.”

PET imaging and tests of cerebrospinal fluid, which document the presence of amyloid beta plaques in the brain, are currently the gold standard for providing a diagnosis of Alzheimer's. But these tests are too expensive and cumbersome to administer to meet the anticipated need for Alzheimer's screening in large populations. Although blood tests that can flag the buildup of amyloid are beginning to emerge from the lab, they are not yet widely available.

For years, primary care physicians have instead relied on pen-and-paper cognitive tests to screen patients with mild cognitive impairment, but these tests can take 20 to 30 minutes to complete and require a trained administrator. The “reality is primary care doctors don't have that time,” says Brad O'Connor, CEO of CogState in Australia.

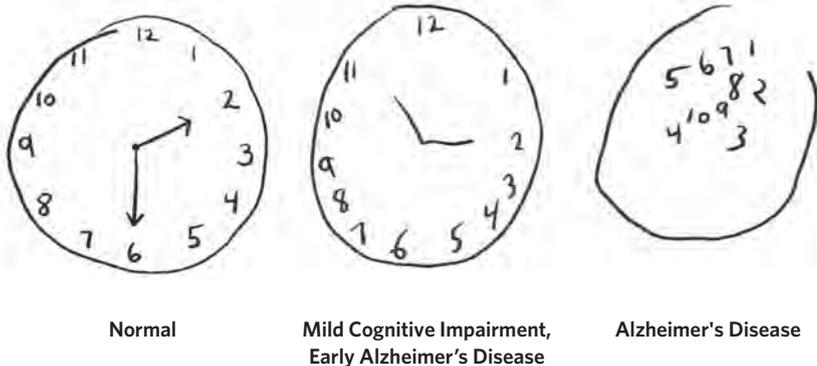
A test sold by Linus Health combines an established pen-and-paper test based on a simple drawing test with added artificial intelligence to make it easier to administer and more powerfully analytic. In the test, a patient is asked to draw a clock with the clock hands indicating a specific time. The task engages disparate areas of the brain involved in motor, visual, analytical and other functions that are often impaired by dementia.

In the original version of the test, the patient draws the clock on a piece of paper, and a trained observer evaluates the results and refers the patient on for further testing. Linus's version, originally developed at MIT and commercialized by a company called Digital Cognition Technologies that

clinics and longitudinal epidemiological studies, including both the Framingham Heart Study and a Rush Hospital study documenting the health of primarily minority populations.

In a study, scientists from Linus and Harvard Medical School found that they could detect signs of cognitive dysfunction in less than three minutes in patients who didn't previously report impairment. The scientists checked each detection with PET scans, which

“The reality is primary care doctors don't have that time” to administer paper-and-pencil tests.



Linus later acquired, has the patient draw the clock using a stylus on the iPad while an AI algorithm tracks the movement of the hands, measuring a wide array of variables, including the time it takes to respond to instructions, the size and characteristics of the drawing itself, and the way the patient moves their hands. The AI algorithm was trained on thousands of patients with dementia of varying severity, as well as healthy people. The data were gathered from local

can reliably identify buildup of amyloid plaque in the brain, a hallmark of Alzheimer's. The paper was published in *Neurology* in 2021.

The assessment is simple enough to do in a primary care practice during an annual wellness visit, administered by a medical assistant with minimal training. The company has raised \$64 million since its founding in 2019 and completed early testing of the product in 2023. The product is now being rolled out in the Indiana University

Health System, at UMass Medical School, at Emory University and in about 50 small medical practices. It has so far been used on several thousand patients.

“We are not suggesting that this is the only cognitive assessment you should ever do, but it's a really low-cost, noninvasive, easy assessment that will identify those first changes and get people at least on the pathway for assessment of the issues—and also conversely conclude this person is not at risk to decline in the next five years. Which really helps doctors with the ‘worried well,’ because they're fine, but they take up a lot of healthcare resources.”

Several other firms are working on digital tests aimed at addressing this growing demand.

CogState plans to roll out Cognigram, in the U.S. early next year. It uses a virtual deck of playing cards, which can be displayed on a computer screen, to assess memory and cognition. The company has partnered with the Japanese drug maker Eisai, the makers of Leqembi, to get it into the hands of doctors.

CogState is perhaps best known for computer-based cognitive assessments designed to measure changes in cognitive function over time. Its Cogstate Brief Battery test, which is widely used in clinical trials, healthcare and academic institutions, uses the digital cards to establish a baseline in areas such as attention, visual learning, and working memory and then tracks changes over time through follow-up assessments. Cognigram, however, does not require a baseline digital assessment for its screening, which allows doctors to identify patients for further tests, says O'Connor. Instead, on its first use, the patient score is compared to an age-matched normative dataset. In subsequent tests, patient scores

are compared to both the normative dataset and previous patient scores.

The test, which can be administered by a medical assistant in a doctor's office or even done remotely from home, performed well in several studies, including one published last year in the *Journal of Alzheimer's Disease* in December. It compared the performance of 4,871 cognitively unimpaired adults to that of 184 adults who met clinical criteria for mild cognitive impairment.

"It all sounds very simple," says O'Connor, "but these tests have been proven to be really sensitive to the earlier stages associated with disease."

Cognivue, based in Victor, New York, recently released a digital cognitive testing technology that first screens for potentially confounding factors like visual and motor impairments, then adjusts the test to account for these impediments, which otherwise can muddy the results. It does so by displaying a bunch of white dots on a black screen contained in a green, wedge-shaped outline. As the dots move in clockwise and counterclockwise directions, the patient is instructed to keep the dots within the green wedge by turning a knob that controls the position of the wedge.

To measure cognitive impairment, the program then asks patients to distinguish real words displayed on the screen from nonwords or to distinguish letters from random symbols. Other tests ask the test subject to distinguish between different shapes. The test increases in difficulty until the subject reaches the limits of their abilities.

The Cognivue program uses AI algorithms to evaluate patient performance in visual acuity, memory, executive function and other areas, as compared to people with similar age, education levels and other demographic factors.

Adam Piore is a freelance journalist based in New York.

Gateway to the Brain

The optic nerve is a link to the brain—and potentially to disease diagnosis.

The big goal for firms that are devising tests for Alzheimer's is to find a simple, inexpensive one that is reliable enough to provide definitive diagnoses—something that could replace entirely the need for expensive PET scans and cerebrospinal fluid biopsies. Scientists at Toronto-based RetiSpec believe that retinal scans might eventually meet this bill.

The eye is linked to the brain by way of the optic nerve, so changes in the brain—including the buildup of amyloid plaque

from Alzheimer's—are reflected in the retina. RetiSpec has developed a device that beams light on to the retina and measures the light reflected back. It then analyzes the output using AI algorithms trained on other retinal scans collected from thousands of Alzheimer's patients who had tested positive on PET and cerebral spinal fluid tests.

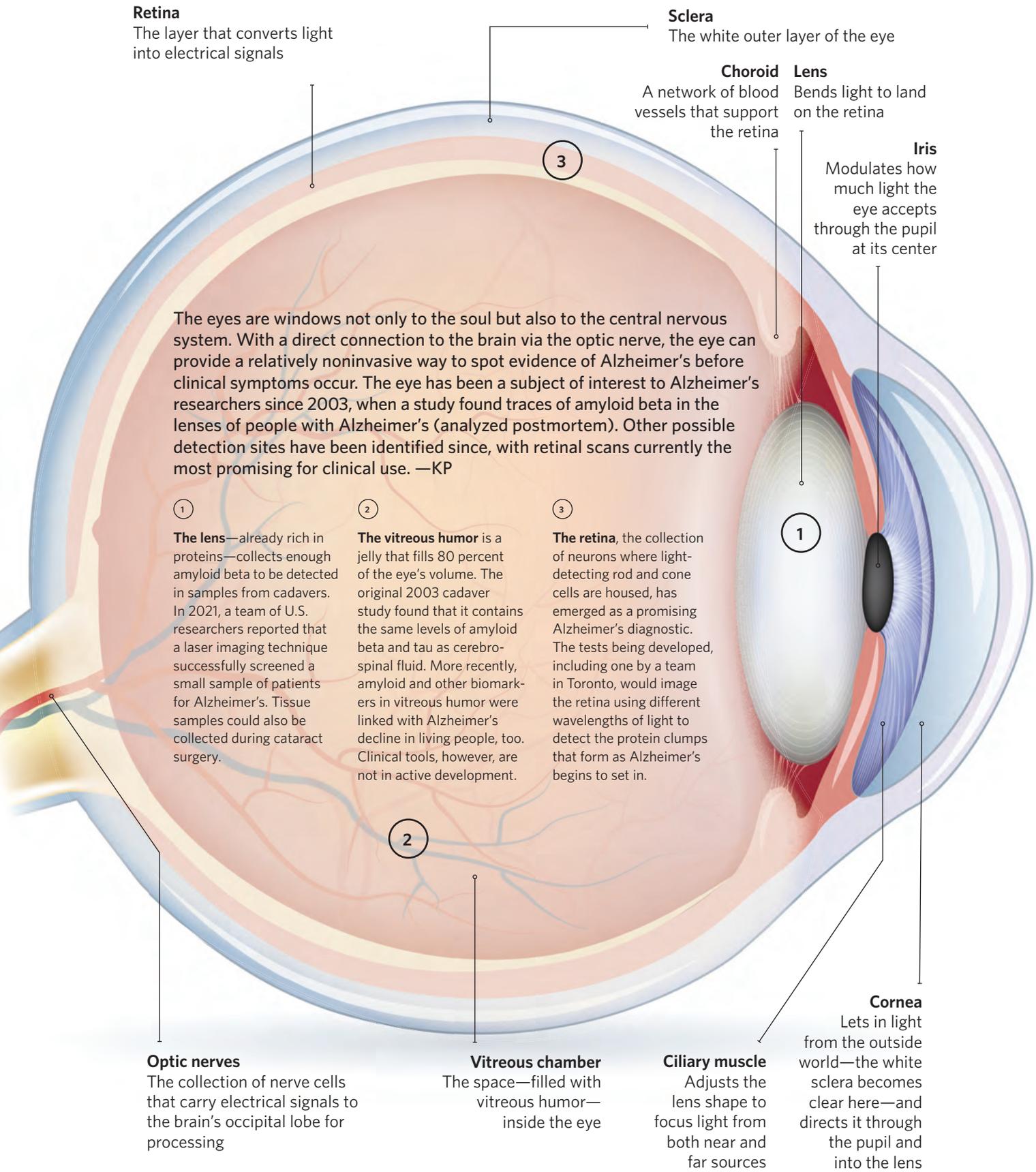
The device is an attachment that can be screwed on to a device, called a fundus camera, that most eye and neurology specialists, and some primary care physicians, already have. Although the compa-

ny has not yet set a price for the device, officials say that the cost per test will fall below \$1,200. Whereas normal fundus cameras capture three wavelengths of color, red, green and blue, the attachment consists of a hyperspectral sensor that can capture a wider band of frequencies, most of which are not visible to the naked eye.

Hyperspectral sensors have detected Alzheimer's disease in lab mice. CEO Eliav Shaked says a multicenter, blinded validation study showing the company's AI-based retinal test can predict amyloid-beta brain pathology in a diverse population of adults with preclinical, mild cognitive impairment, and probably Alzheimer's disease, is under review at a scientific journal.

RetiSpec hopes eventually to win FDA approval for use as a diagnostic tool, rather than just for purposes of screening. Retinal scans, he says, are more convenient than blood tests because they can provide a diagnosis immediately and don't require the use of sensitive diagnostic equipment currently needed to analyze blood samples. The company is testing the device at 20 clinics and doctor's offices, in partnership with Evergreen Health and Advent Health. It is slated to begin feasibility testing with the FDA in early 2024. Shaked expects the technology will be available in early 2025. —AP

"It all sounds very simple, but these tests have been proven to be really sensitive to the earlier stages associated with disease."



Retina

The layer that converts light into electrical signals

Sclera

The white outer layer of the eye

Choroid

A network of blood vessels that support the retina

Lens

Bends light to land on the retina

Iris

Modulates how much light the eye accepts through the pupil at its center

The eyes are windows not only to the soul but also to the central nervous system. With a direct connection to the brain via the optic nerve, the eye can provide a relatively noninvasive way to spot evidence of Alzheimer's before clinical symptoms occur. The eye has been a subject of interest to Alzheimer's researchers since 2003, when a study found traces of amyloid beta in the lenses of people with Alzheimer's (analyzed postmortem). Other possible detection sites have been identified since, with retinal scans currently the most promising for clinical use. —KP

1

The lens—already rich in proteins—collects enough amyloid beta to be detected in samples from cadavers. In 2021, a team of U.S. researchers reported that a laser imaging technique successfully screened a small sample of patients for Alzheimer's. Tissue samples could also be collected during cataract surgery.

2

The vitreous humor is a jelly that fills 80 percent of the eye's volume. The original 2003 cadaver study found that it contains the same levels of amyloid beta and tau as cerebrospinal fluid. More recently, amyloid and other biomarkers in vitreous humor were linked with Alzheimer's decline in living people, too. Clinical tools, however, are not in active development.

3

The retina, the collection of neurons where light-detecting rod and cone cells are housed, has emerged as a promising Alzheimer's diagnostic. The tests being developed, including one by a team in Toronto, would image the retina using different wavelengths of light to detect the protein clumps that form as Alzheimer's begins to set in.

2

1

Optic nerves

The collection of nerve cells that carry electrical signals to the brain's occipital lobe for processing

Vitreous chamber

The space—filled with vitreous humor—inside the eye

Ciliary muscle

Adjusts the lens shape to focus light from both near and far sources

Cornea

Lets in light from the outside world—the white sclera becomes clear here—and directs it through the pupil and into the lens

[INFOGRAPHIC]

Risk Factors for Alzheimer's

Genes and age play a big role in susceptibility to the disease, but choices make a difference, too.

Scientists are still learning about the causes of Alzheimer's, but most agree that many factors contribute to an individual's risk of getting the disease. Some risk factors, such as age and genes, are inescapable. Others can be modified with lifestyle changes, such as exercise and nutrition—in one study, participants were able to reduce their risk of getting Alzheimer's by 60 percent. Although most risk studies focus on dementia in general, here are important findings about the known risk factors as they apply to Alzheimer's. —KP

KEY

Risk factors—marked ▲—are arranged by category and listed in order of importance.

Squares mark the proportion of cases attributable to a modifiable risk factor:

■ ■ ■ ■ ■ ■ ■ ■ Most (8 percent)
 ■ ■ ■ ■ ■ ■ ■ ■ Least (1 percent)

Genetics

Researchers have identified more than 70 genes associated with Alzheimer's. Some increase risk, while at least one protects against it. Almost none guarantee their carriers will (or won't) develop the disease.

▲ **Familial Alzheimer's**
 This inherited form of the disease accounts for fewer than 1 percent of cases, most beginning before age 65.

▲ **APOE4 and other genes**
 Genetics is the main factor in 60 to 80 percent of Alzheimer's cases, researchers estimate. The most widely studied gene, APOE4, seems to slow the brain's ability to clear amyloid beta and to make tau tangles easier to start forming. Dozens of other genes are implicated as well, and the list continues to grow. The best defense is to detect the disease in the early stages.

Environment

Recent years have identified air pollution as a major risk factor. (Aluminum, once thought to be a major culprit, has been cleared of blame.) Other factors, such as radiation, noise and climate change, may also play a role.

▲ **Air Pollution**
 Tiny particulates from cars, smokestacks and forest fires can pass from the nose to the brain, where they may promote amyloid deposition.

Brain Health

Because Alzheimer's degrades and eventually kills neurons, a healthy brain is one of the best defenses.

▲ **Lack of schooling**
 Educational attainment—particularly before age 20—correlates strongly with decreased risk of dementia in adulthood.

▲ **Depression**
 People who show depressive symptoms in a screening are twice as likely to develop dementia.

▲ **Traumatic brain injury**
 Significant damage to the brain, such as from car accidents, sports injuries and falls, modestly increases dementia risk.

▲ **Cognitive reserve**
 A sharp, curious mind may help stave off some of the cognitive decline of Alzheimer's disease. In the 1980s, researchers found from autopsies of older adults that the brains of some highly intelligent, mentally active people with no signs of dementia still harbored the plaques and tangles associated with Alzheimer's. They reasoned that "cognitive reserves" allow the brain to adapt to these physical changes by finding alternative pathways for thinking and recall. Recent studies suggest that having high levels of cognitive reserve, developed over a lifetime of stimulation and curiosity, reduces the risk of symptomatic Alzheimer's by about 40 percent. Brain health, it seems, matters.

Source: Risk factor relative importance: G. Livingston et al., *The Lancet*, 396, 413 (2020).

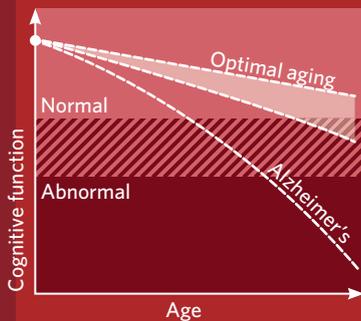


Age

Past age 65, the rate of Alzheimer's doubles every 5 years; one-third of people over 85 have the disease. Age is the single most important risk factor identified for late-onset Alzheimer's (about 85 percent of cases). Age is beyond our control, but watching for early symptoms and intervening as soon as possible to slow the disease's progression improves outcomes. For a list of early signs of dementia, see "How to Detect Alzheimer's Before Symptoms Appear," on page 47.

Normal brain aging

Mild cognitive decline occurs naturally with age, but people with Alzheimer's typically see a much faster drop-off.



Source: "Alzheimer's Disease and Other Dementias," Mayo Clinic, 2020.

Lifestyle

An active, healthy lifestyle protects against Alzheimer's and other dementias, though it's difficult for scientists to determine precisely how. These factors have well-established links.



⚠ Social isolation

Social contact—through friendships, family, marriage and work—seems to provide long-term cognitive benefits, including reduced risk of all dementias.



⚠ Alcohol Use

One large study in the U.K. found that for heavy drinkers, every seven additional drinks per week increased dementia risk by 17 percent.

The case for sleep

Studies in mice have shown that cerebrospinal fluid in the brain and spinal cord acts during sleep to clear amyloid beta. Another study followed 8,000 Britons for 25 years and found those who got six or fewer hours sleep in their midlife years were 30 percent more likely to develop dementia.

Weak links

Studies have provided hints that the following factors may also lower dementia risk (though so far solid evidence is lacking):

- Maintaining good eyesight
- Living in a quiet neighborhood
- Preventing gum disease
- Following a Mediterranean diet
- Speaking two languages
- Keeping blood iron levels healthy
- Staying current with vaccinations
- Sitting less than 10 hours a day
- Spending time in nature
- Avoiding certain laxatives and acid reflux medications

Body Health

Poor physical health can raise the risk of Alzheimer's. Here are six ways for which evidence is strong.



⚠ Hearing loss

People who lose their hearing in middle age are about twice as likely to develop dementia. Regular testing and use of hearing aids (if needed) can lower risk, though evidence is weaker for Alzheimer's.



⚠ Smoking

People who have never smoked developed Alzheimer's two-thirds as often as smokers and ex-smokers. Quitting makes people less likely to develop other dementias.



⚠ Hypertension

High blood pressure increases the risk of all dementias, but treating the condition with drugs lowers the likelihood of cognitive decline. Anti-hypertension medication seems to slow the progress of Alzheimer's.



⚠ Physical inactivity

People who exercise regularly in middle age reduce their Alzheimer's risk by 45 percent, one meta-analysis found.



⚠ Diabetes

People who have had type 2 diabetes develop dementia at higher rates—1.6 times as often for men, 1.8 for women. It's not yet clear whether medications reduce that risk.



⚠ Obesity

A body-mass index of 30 or higher is correlated to a higher risk of dementia.



A Grassroots Approach to Diversity

Community-based programs are working to reverse decades of underrepresentation by building trust among clinicians, researchers and everyday people.

BY SIMAR BAJAJ

A vibrant, stylized illustration of diverse people. In the foreground, a young man with dark hair and a serious expression looks forward. Behind him, a woman with blonde hair and glasses is partially visible. To the right, a woman with dark hair and a red top is shown. In the bottom right, a young man with dark hair and a slight smile looks towards the viewer. The background is a mix of warm and cool colors, creating a sense of community and diversity.

When Chris Tann was diagnosed with frontotemporal dementia, he and his wife Debra drove seven hours, each way, to Vanderbilt University in Tennessee to participate in a clinical

trial, returning several times each year for follow-up visits. Clinical research in or around their community in Valdosta, Georgia, was virtually nonexistent.

Debra Tann, who is a certified dementia educator, has a front-row seat to the disproportionate impact Alzheimer's disease and related dementias have in communities of color. She has lived in Valdosta, a city of 56,000, whose population is primarily Black,

“Brain health equity begins in the lab.”

for three decades and has made it her mission to educate and empower members of her community to participate in clinical research. Be-

yond simply promoting equity, what's at stake is the development of tailored treatments that could help stop dementia in communities of color nationwide.

Clinical trials have long been hindered by a lack of diversity, where people of northern European descent are significantly overrepresented and Black, Latino, Asian and Indigenous peoples are left out. This problem is especially acute for Alzheimer's disease. For example, the phase 3 trial of the promising new drug donanemab enrolled 1736 people, but only



35 Black and 59 Hispanic participants, representing 5 percent of the study. Likewise, lecanemab, the first Alzheimer's drug to receive full approval by the U.S. Food and Drug Administration, was tested in a 1,795-person trial, but only 2.5 percent of the participants were Black and 12.5 percent Hispanic.

Across more than 100 Alzheimer's drug trials, 95 percent of participants were white, a percentage that's remained stubbornly high over the past 20 years. The lack of representation may be even greater than these numbers would suggest because Black patients are twice as likely as white patients to have dementia, while Hispanic patients are 1.5 times as likely. "The vast amount of our research and understanding of Alzheimer's—and other related dementias—are based on these rarefied, highly educated, high socioeconomic status, non-Latinx white samples," says Monica Rivera-Mindt, a professor of psychology at Fordham University.

Despite their higher rates of dementia, people of color more often fail to qualify for trials than white people. In general, marginalized groups are ruled out because they have a higher rate of comorbidities and their blood screenings reveal lower levels of Alzheimer's pathology than white people with similar disease progression. In addition to steering Alzheimer's research and development away from people of color, these disparities draw into question our understanding of the disease itself. "It's a terrible waste of time, efforts and resources to start going down the wrong path for the next 30 years because we don't understand

the differences in disease biomarkers between people of differing ancestries," says Nancy Lynn, a senior vice president at the BrightFocus Foundation and co-leader of the project engaging local communities in Alzheimer's research in Valdosta. "Brain health equity begins in the lab."

Reversing decades of underrepresentation is not a short-term project, and it involves years of building trust among clinicians, researchers and everyday people. Through community-based programs, scientists and activists are beginning to do the work of bridging the gap between the medical establishment and local communities. The program in Valdosta and another in Rio Grande City, Texas, demonstrate the need to move beyond a one-size-fits-all approach and toward a more personalized model for Alzheimer's clinical trials.

Community-led trials

Even though Starr County, Texas, has the country's highest dementia rate—more than a fifth of Medicare beneficiaries are affected—Alzheimer's clinical trials had never been conducted in the county. In 2021, however, the El Faro Health and Therapeutics opened its doors with the mission of enlisting the community of Rio Grande City, an overwhelmingly Hispanic enclave, in clinical trials.

The clinic was started by Antonio Falcon, a trusted healthcare professional and a pillar of his community. When his son, James Falcon, returned home after serving as an emergency room physician in the U.S. Army, they decided to tackle the challenge of bringing local residents into the mainstream of Alzheimer's research.

With support from the Global Alzheimer's Platform, El Faro has focused on providing more opportunities for Latinos to participate in Alzheimer's research. Jessica Cantú, a nurse practitioner and the site director, hosts community events twice each month, where she explains to members of the community how "research" differs from "experimentation," how safeguards like consent forms protect participants, and why it's important to be represented in clinical trials. "I always tell them: We got Tylenol and Ibuprofen. How did we get them? They had to be researched," she says. "You may not know that

"We got Tylenol and Ibuprofen. How did we get them? They had to be researched. You may not know that because us Hispanics weren't asked to participate in this research."



“All we do is educate, educate, educate. We’re from here, so most people either know our parents or grandparents, so they’re able to say, ‘Okay, they are so-and-so’s daughter. I trust them a little more.’”

because us Hispanics weren’t asked to participate in this research.”

Cantú has also helped launch several clinical trials, including one that tests whether donanemab can prevent Alzheimer’s. Funded by Eli Lilly, this trial is enrolling 65- to 80-year-olds who have evidence of amyloid plaque in their blood, an Alzheimer’s biomarker, but no dementia, to determine whether donanemab can slow Alzheimer’s progression when compared to placebo.

For people who don’t meet the inclusion criteria for these trials, El Faro has launched an observational study open to anyone 18 and older, where people take memory tests on their phone or computer every three months. Part of a larger global study funded by the Davos Alzheimer’s Collaborative, the El Faro study is a digital phenotyping study, which uses data from personal digital devices to study human behavior with the goal of better understanding the causes of dementia.

Educate, give, then enroll

In Tann’s community in Valdosta, a third of households make less than \$20,000 a year. A lack of public transportation and healthcare providers who are people of color are additional barriers to accessing quality healthcare, as well as significant levels of mistrust in the healthcare system, stemming from a long history of discrimination and structural racism. Tann, who founded a dementia advocacy group called Reminiscent, says that many of her neighbors associate “research” not with hope and opportunity,

but with past atrocities such as the Tuskegee study of untreated syphilis and a legacy of transactional arrangements. An effort to immediately try and enroll residents would likely have failed.

As a result, Tann is focusing first on educating people about dementia, partnering with them, and winning their trust. For two years, with support from BrightFocus Foundation, she has held more than 100 community events in Valdosta, ranging from dementia-specific activities like educational workshops and quarterly brain health screenings to more general community-building exercises. These include offering complimentary fitness classes for community members, producing free informational webinars specific to Valdosta, hosting community dinners and a holiday party for elders, organizing a Respite Cruise for caregivers, and providing dementia training for professionals and families.

The ultimate goal is to bring a brain health center to Valdosta that will conduct clinical trials, train providers in dementia, and

engage everyday people in prevention. By partnering with the community to provide these health-promoting activities, the Valdosta program aims to establish trust and educate people about brain health, likely offering spillover benefits for other conditions like diabetes and cardiovascular disease.

“We are taking ‘the backdoor approach,’” Tann says. “We are not in the face of our community; we’re tiptoeing in to find out where they are.”

Building trust and understanding requires moving at the pace of the community, rather than following a specific mandate. For now, Tann plans to begin recruiting community members in mid-2024 for a research study that people can participate in from their homes.

Simar Bajaj is a freelance writer.

“We need genomics at a global scale”

Elias Zerhouni says expanding research to include a diverse cohort is essential to beating a disease that is far more complex than researchers understood two decades ago.

BY FRED GUTERL

ILLUSTRATIONS BY OBOH MOSES

When Elias Zerhouni took over as director of the National Institutes of Health in 2002, the only way doctors could know for certain whether a dementia patient had Alzheimer’s disease was to perform an autopsy.

A few years later, new technologies that could deliver a definitive diagnosis revealed an embarrassing truth: many of the ongoing clinical trials for Alzheimer’s treatments included a significant number of subjects who had been misdiagnosed. “We didn’t know who had the disease and who didn’t have it,” Zerhouni recalls.

It fell to Zerhouni and his colleagues at NIH to fashion a research program that could exploit the power of the new diagnostic technologies—which now include imaging, biomarker tests and digital cognitive tests, among others—to learn about what has turned about to be a hugely complex disease.

Since leaving NIH in 2008, Zerhouni has carried on that work in various roles—as head of research at Sanofi from 2011 to 2018 and, currently, as a founding board member of the Davos Alzheimer’s Collaborative (DAC). He is helping DAC assemble a cohort of Alzheimer’s patients that reflect the world’s genetic, environmental, social and economic diversity, which he believes is crucial to understanding and treating the disease.



DAC's Global Cohorts program has so far engaged 26 different countries, with the goal of drawing up to one million people from rich and poor nations alike in North America, South America, Africa, Europe, Asia and the Middle East.

Expanding research to include a diverse cohort is essential to treating Alzheimer's disease, he believes. Still, new drugs that can slow the progress of Alzheimer's, despite their limitations, are a turning point, and bode well for the future. "Progress in medicine tends to occur like a swarm around a fortress," he says. "When there is a crack in one place, you have a lot of people going through that crack, not knowing if it's a dead end or if it's the beginning of redemption."

Scientific American Custom Media talked with Zerhouni about the last two decades of Alzheimer's research and his vision for what needs to happen going forward.

SCIENTIFIC AMERICAN CUSTOM MEDIA:

You've had a bird's-eye view of many different human diseases. How is Alzheimer's unique?

ZERHOUNI: A perfect life is: you are born, you're healthy, you remain healthy, and you die.

However, that's not what you see. What you see is that you have a healthy beginning after childhood illnesses, you're pretty healthy until about 50, when there are some cancers. For many people who live longer and remain physically healthy, cognitive impairment because of neuronal degeneration leads to a more profound loss of quality of life.

Alzheimer's is a slow pandemic. It's growing along with the prevalence of obesity and diabetes and with aging populations almost worldwide. It has a huge econom-

ic impact—a permanent impact, because you have a population of patients that could have been healthy and self-sufficient but no longer are.

We found that if you delayed the onset of Alzheimer's disease by five years, it would reduce its burden on society by 50 percent. We also found that the mortality of caregivers—the wife who takes care of the husband and vice versa—is extremely high.

If you do not have a functioning neural system, you can't have a functioning body. That's not

"Progress in medicine tends to occur like a swarm around a fortress. When there is a crack in one place, you have a lot of people going through that crack, not knowing if it's a dead end or if it's the beginning of redemption."

just Alzheimer's, it's neuroscience generally. The number-one cause of disability between the ages of 25 and 44 is depression. The impact of a cognitive deficit is often much greater than the impact of a physical deficit.

Why is the medical field so excited about the recent treatments for Alzheimer's?

It's the first crack in the mystery of the disease. In medicine, progress is never a delta function, where you have no treatment and then all of a sudden you have a treatment.

HIV is a good example. We were desperate in the mid-1980s. People were dying right and left. And then we had a cancer drug called AZT that had some effects. It showed that it was doable. It changed the paradigm.

At the time, no one thought that a drug, a small molecule,

could stop a virus. After that, a lot of researchers said, "Wait a minute, maybe we can develop a better AZT. Maybe I can get one against this part of the virus or that part of the virus." Today, you have triple therapies that control the disease for years.

After years of disappointment, the news about Alzheimer's research has only recently gotten brighter. How did we get here?

When I became NIH director in 2002, we could see the evolution

of the disease when it became clinically relevant and clinically obvious. We had no idea what happened before you were symptomatic. When I reviewed the [NIH research] plans for Alzheimer's, I said that we would be unlikely to reverse a disease process that has destroyed so much of the brain's tissues, [including the] neurons important for memory and behavior. It's almost like waiting for the plane to crash and then trying to put it back together.

By 2018, after spending \$20 billion on clinical trials, all the phase 3 trials of the major companies failed. People were desperate, wondering what went wrong and what happened. By then I had become head of R&D for Sanofi, a major pharmaceutical company, which had a program for Alzheimer's disease. I found the same issues. We had no ability to truly diagnose the disease properly. We

had no biomarkers. We couldn't do a biopsy of the brain to confirm a diagnosis, like you can do in cancer. We didn't know who had the disease and who didn't have it.

On top of that, almost all the research was being done on Caucasians and on patients in rich countries. The knowledge base was fragmented, incomplete and incoherent.

Is that when you realized that Alzheimer's researchers needed to study a larger and more diverse population?

At NIH, we funded quite a few investigators looking at Alzheimer's disease. As we did this, we realized that every investigator had a few hundred patients here, a couple thousand there, 500 over here, and so forth, all around the world. But nobody had the critical mass of patients you need to understand variations between individuals and what drove those variations.

As biomarker tests improved, we realized that in many of the trials, perhaps 30 percent to 40 percent of patients did not have Alzheimer's disease. They had dementia from other causes. We had an incomplete hypothesis in a group of patients who don't even represent the disease we're studying.

Was there any value in that work?

When we looked at the data on thousands of patients from the various phase 3 trials, all of the patients who had had a response to treatments were early-stage Alzheimer's patients who had only just started to develop symptoms. Patients who had established memory impairments did not improve. That told me that my analogy—that you can't put a crashed plane together again—was true. It also told me that you could prevent

a plane crash if you knew that the engines were having trouble early enough to make a correction.

About this time, George Vradenburg asked me to speak to a meeting in Lausanne with a specific question in mind: "Don't talk to us about what didn't work. Don't talk to us about what failed. Just tell us what ideas you think we should really consider to advance the field."

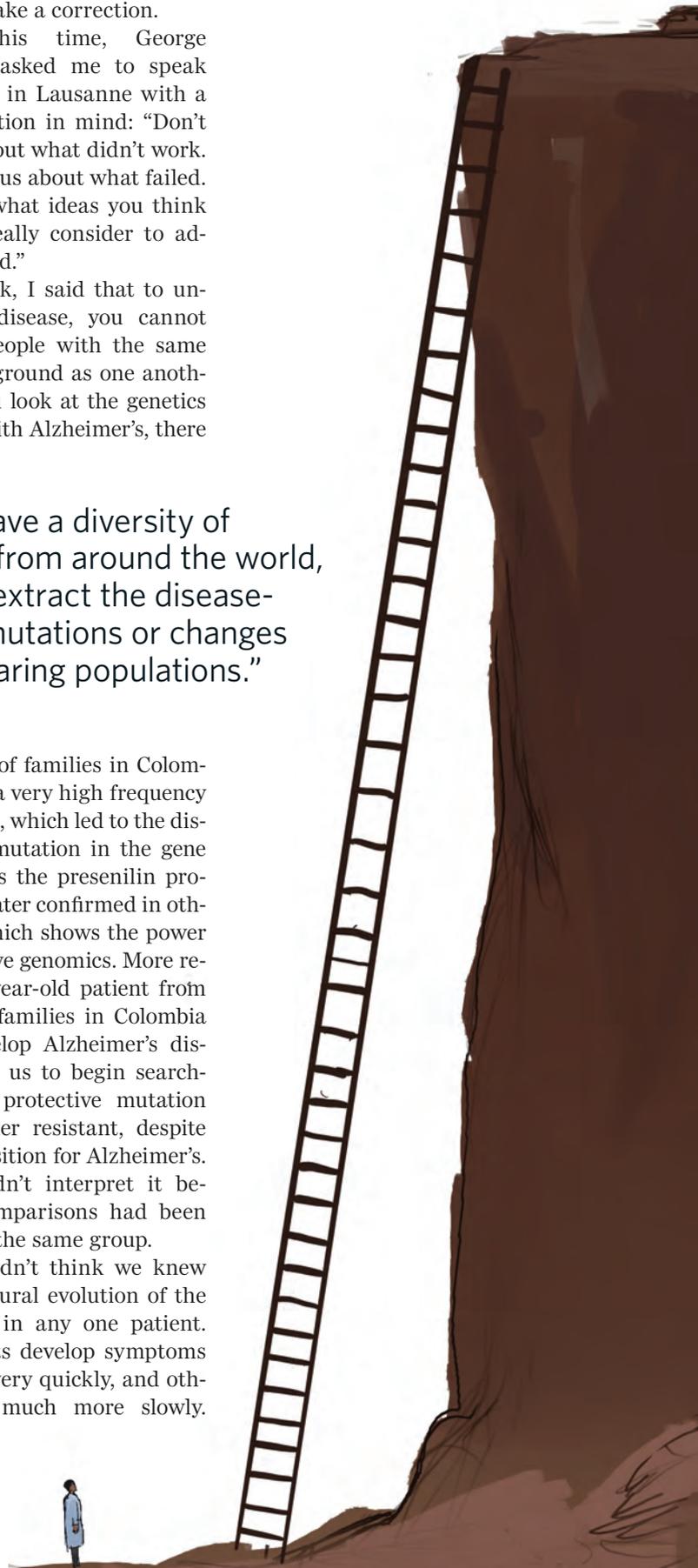
In the talk, I said that to understand a disease, you cannot just study people with the same genetic background as one another. When you look at the genetics of patients with Alzheimer's, there

"If you have a diversity of patients from around the world, you can extract the disease-related mutations or changes by comparing populations."

was a group of families in Colombia that had a very high frequency of the disease, which led to the discovery of a mutation in the gene that produces the presenilin protein. It was later confirmed in other groups, which shows the power of comparative genomics. More recently, a 73-year-old patient from the affected families in Colombia did not develop Alzheimer's disease, leading us to begin searching for the protective mutation that made her resistant, despite her predisposition for Alzheimer's.

You couldn't interpret it because all comparisons had been done within the same group.

Also, I didn't think we knew what the natural evolution of the disease was in any one patient. Some patients develop symptoms and decline very quickly, and others decline much more slowly.



“If you delayed the onset of Alzheimer’s disease by five years, it would reduce its burden on society by 50 percent.”

Why? That’s the central question in Alzheimer’s research. Are there unknown protective mutations that could be exploited for novel therapeutics? I had the sense that we didn’t quite understand what was going on and that we needed to find out by studying a more diverse global population.

The number-one rule in drug development is: understand the biology. The number-two rule is to understand the epidemiology of the disease—when do you intervene? The third rule is, do you have the right population in your trial?

What needs to happen going forward to get Alzheimer’s to the point where it’s a manageable disease?

We need genomics at a global scale. That allows you to compare and separate environmental effects versus disease effects and discover protective mutations. That is why we want to expand DAC’s Global Cohort program to include 100,000 people.

If you have a diversity of patients from around the world, you can extract the disease-related mutations or changes by comparing populations. You can also exclude environmental factors. For instance, people in Africa have a much lower incidence of colon cancer than people in America. Research has found that the heavily meat-driven diet of the developed

world is driving the incidence of cancer. By comparing environmental effects around the world, you can come up with conclusions and discover what is driving the disease in the first place, as we did for hypertension and cholesterol.

Solving Alzheimer’s is like scaling a 100-foot cliff, and we have ten 10-foot ladders. Wouldn’t it be better to put them together and have a 100-foot ladder so we can get over the cliff?

If you found a patient with this disease who had the same genetic background as someone else, and one of them was a fast progressor and one of them was a slow progressor, you’d ask: “What is protecting the slow progressor from declining faster?” This is what we look for in genomics. By looking at the genome of all these patients and comparing them, we find mutations that are protective. That’s important for discovery and for treating this disease.

How many people do you have now in the Global Cohorts program?

22,000—it’s the largest cohort in the world right now.

What is the challenge of getting to 100,000?

It’s multifactorial. First of all, Alzheimer’s is a long, chronic disease. We want to focus on existing cohorts that have followed patients for a long time already. You don’t just go in and say, “Who wants to do this research?” and then wait for 20 years before you have the cohort. We’re trying to build on what is already existing that has enough of a longitudinal timeline that will essentially make the 100,000 we select very powerful immediately.

Second, quality has to be standardized. We have to have a central lab for blood tests. That requires

a lot of collaboration, cooperation and negotiation. For example, China does not allow the export of DNA from Chinese citizens. So, we have to have a lab in China, but then we have to have an agreement that the data will be shared.

Every center we’ve approached has been willing to share data in a federated way. Gates Ventures is funding our digital backbone and data analysis and is willing to provide the framework. Ethics is also important. You absolutely have the obligation to get informed consent, especially if you do new types of studies. That takes time.

There is also a clinical trial network, in parallel to the cohort, which is pre-positioning interested scientists worldwide to be able to conduct proof of concept trials quickly. A study of 1,000 patients is ongoing to test the various biomarkers that are being proposed, so that we can select the best ones, including novel digital biomarkers using smartphones, for the cohort. It’s a heavy lift that requires a lot of time and resources.

Aside from assembling a large cohort, what else needs to be done?

When do you know if someone has the disease and will develop a more severe form? Discovering biomarkers is critical. If you think that your therapy is only effective early in the disease, then you need to have a reliable way of detecting who that is who deserves the treatment. To do that, diversity is important because blood is not the same blood everywhere in the world.

What about digital biomarkers?

Typically, when you want to diagnose mild cognitive impairment, you use a series of tests. The doctor gives you seven words to memorize, makes you do something

else, and then 15 minutes later, asks you again. Other cognitive tests focus on ideation, rational ability, and so on. They are all dependent on cultural context—on where the test is given and what doctor or nurse administers the test. It's an extremely noisy signal. This makes it difficult to categorize patients in a meaningful way.

A digital biomarker is, you take your cell phone and I ask you to type in a few words. I can measure the speed at which you type and I can measure it over time. It's an objective measure. We know from research that a person's voice print changes with the onset of Alzheimer's disease. So does the ability to verbalize. We can measure them and, with artificial intelligence, we can classify it.

A researcher in England used the U.K. Biobank, which has accumulated 500,000 patients over the past 25 years. Then they asked the question, who among those patients developed Alzheimer's disease? We know that a mutation called APOE4 is a good predictor of whether or not you will develop Alzheimer's disease. This researcher recorded the voices for a whole series of patients and, lo and behold, the voice print analysis could actually detect the patients that had APOE4 mutations.

There are many factors that contribute to Alzheimer's disease that need to be discovered. The cohort program of DAC is creating a critical mass of diverse patients that represents the global nature of the disease and that can be used to separate environmental effects from biological ones and discover clues to protective mutations.

As you look at large populations, you immediately realize that what we call Alzheimer's disease is not one disease, it's multiple diseases that each have very different outcomes. To have a one-size-fits-all

approach to this complex disease does not serve us well. Many in the field are coming to the conclusion that there may be at least two kinds of Alzheimer's: inflammatory and noninflammatory types.

We've talked a lot about genetics as a risk factor. What would you like to know about environmental or geographic factors?

What I would like to know is whether there is differential incidence in different countries. Is the U.S. getting a higher incidence of Alzheimer's than people in Uganda? And if so, why?

Is there any feeling that environmental factors play a big role in Alzheimer's?

[Laughs.] It's hard to think it will be environmental. Alzheimer's was discovered a century ago. Unlike heart disease, which was low in the early part of the century and then became high and deadly in the '50s, '60s and '70s, we haven't seen that in Alzheimer's. We are seeing more Alzheimer's because life expectancy has gone up. But I'm not seeing a complete change—a complete delta. When you see a delta in epidemiology, that's when you suspect an environmental cause.

But there has been a rise in obesity and heart disease, which are linked to Alzheimer's.

Yes, there are certainly aggravating factors, no question about it. Lack of exercise, lack of mental stimulation, obesity, sedentari-ness, loneliness, mental health—all of those are aggravating factors. I don't think that they're causal, but that is my opinion. The one thing you have to learn in this business is humility because the mystery is bigger than all of us.

What would you tell someone who was diagnosed with early-stage Alzheimer's right now?

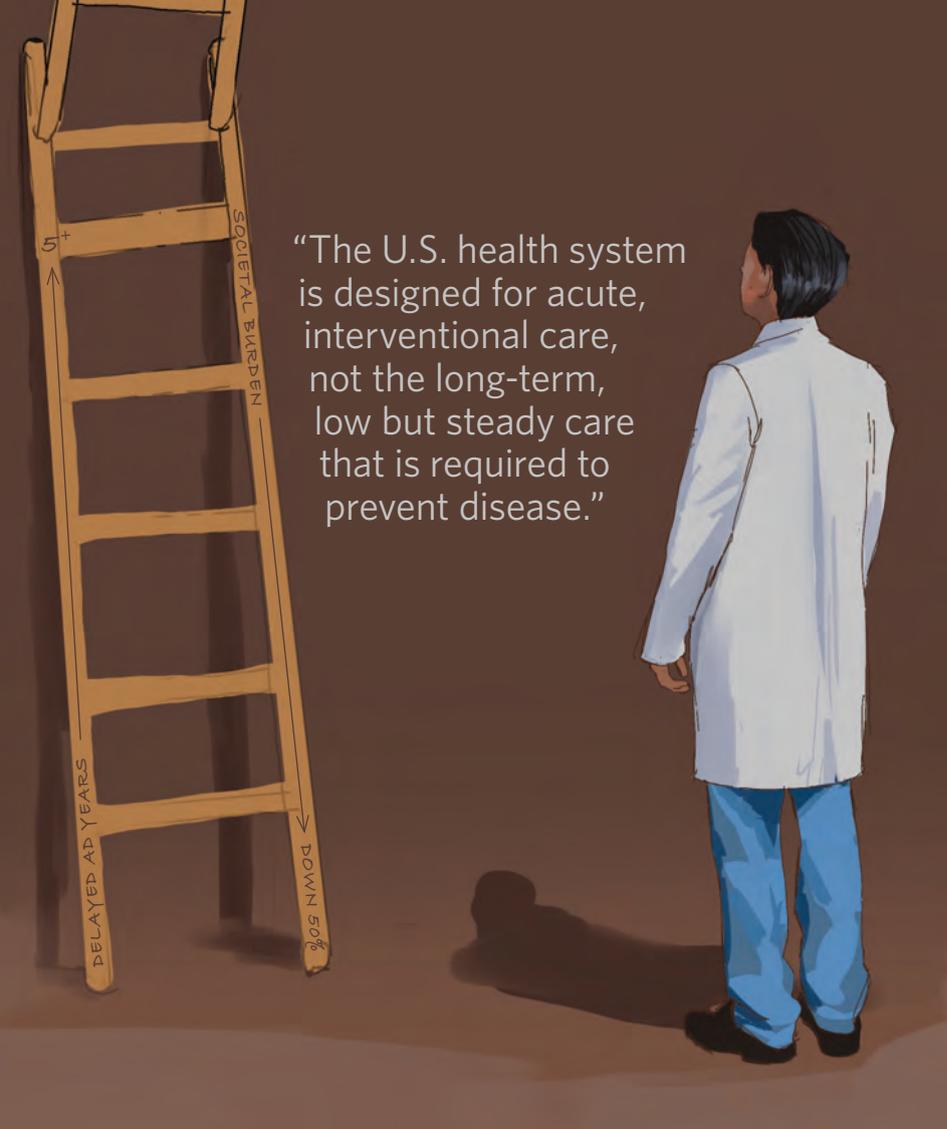
The cofactors need to be acted upon—if you have heart disease, diabetes, obesity, you absolutely need to put yourself in a good health status. We also know that some medications can delay [the onset of symptoms], but they are only effective for a year or two.

It all depends on the age of onset. If the age of onset is 75 or 80—like President Reagan, for example—you can manage it for three to four years. If it happens earlier, that is where the need for new therapy is. You could propose [taking] antibodies that have just been approved, but we know that it's about 18 months to stabilize, and we don't know what the long-term slowdown of the disease would be.

Is the U.S. healthcare system adequate to tackle Alzheimer's?

It's an absolutely critical question. The U.S. healthcare system is not geared towards prevention. There is also a lack of preparation of the healthcare system to deal with a slowly growing chronic disease. And that is a focus of the healthcare preparedness component of DAC. Look at obesity—we're not dealing with it. Do you think we're dealing with diabetes? We're not dealing with it. The U.S. health system is designed for acute, interventional care, not the long-term, low but steady care that is required to prevent disease.

Prevention is not paid for in our system. Why? Because in large part insurance companies change clients every year or two. If you are an insurance company and you say, "I'll pay for your prevention," next year you'll be someone else's client. I don't know that I have a



“The U.S. health system is designed for acute, interventional care, not the long-term, low but steady care that is required to prevent disease.”

solution, but clearly Alzheimer’s is going to present a conundrum because it’s a disease that requires early intervention to prevent damage later on, a little bit like diabetes and heart disease.

Is there anything that the U.S. government should be doing?

Yes. There is not currently a mechanism to have a “Manhattan Project” approach to a disease like this, but we should consider it. We’ve done it with HIV. But Alzheimer’s doesn’t seem to get the energy at this point. The National Institute of Aging has received more funding, and that’s good. DAC has applied for a grant to the NIH to be able to support the cohort, and I think there is receptivity. We want

to provide a phased, milestone-based approach to the program.

What would a Manhattan Project in the U.S. for Alzheimer’s look like? Does any other country have one?

The U.K. comes closest because of the 500,000 patients they’re following in [the U.K.] Biobank. The problem is lack of diversity. We have a program called All of Us, in which a million Americans will be completely sequenced and analyzed. The problem with that is that you may not have enough patients in any one group to reach solid conclusions—a million people with 1,000 diseases, few of which have a critical mass. You’ll have enough critical mass to study obesity, but

I don’t think you’ll have critical mass for early Alzheimer’s disease.

It would have some value because then you can compare the genomes of people with Alzheimer’s with people who have no Alzheimer’s. But it’s not comprehensive enough and integrated enough around this disease process.

And remember, the economic impact of Alzheimer’s is huge, in addition to the huge cost to health.

The U.S. alone wouldn’t really be able to have a Manhattan Project, because of the lack of diversity. You really do need the breadth of a global effort.

That is my position, yes.

Unlike cardiovascular disease or cancer or many other diseases, there’s something taboo about the brain. You cannot biopsy the brain. You cannot really invasively study the normal brain or the Alzheimer’s brain. We biopsy cancers all the time, we put catheters all around the vessels, we’ve developed angioplasty and stents and so on and so forth. But the culture of neuroscience is much more conservative. Even though we know that the micro-biopsy of the brain is doable without being life-threatening or mind-altering, we have an aversion to it. For example, simple spinal taps are well accepted in Europe but not in the U.S., which greatly hampers research in Alzheimer’s disease.

If you look at the history of medicine, the heart used to be taboo as well. In the ‘30s, doctors felt that if you tickle the heart with the catheter, it would stop. It was dogma that you couldn’t touch the human heart, until a cardiologist in Austria, Werner Forssmann, did it and got the Nobel Prize for it. We are at the same stage in neuroscience as we were in the 1930s with cardiology. ■



The Urgent Challenge of Scale

To bring new tests and treatments to the people who need them, healthcare systems must transform how they approach dementia care.

BY HILARY EVANS AND JOHN BELL

Dementia robs us of everything that matters. Our memories. Our connections. Our story. Every three seconds, another person in the world hears the devastating news that they have dementia. No wonder, then, that it is the most feared condition among people aged over 55.

But, after decades of relentless research across the globe, that is all set to change.

Investments in dementia research are finally leading to breakthroughs, as life-changing treatments that may slow the progression of Alzheimer's come within close reach. And we're understanding more and more about how we can reduce our risk of developing dementia. This progress is mirrored by active and growing investment in drug development in the

field of neurology around the world, which is fueling further innovation and drug discovery.

For a field that has seen no progress since the 1990s, when symptomatic drugs in the form of cholinesterase inhibitors were introduced, it certainly does feel that the time to turn the tide on this devastating condition has finally arrived.

The power of recent scientific discoveries, coupled with lessons from a litany of past research failures, means there is now a new sense of urgency on both sides of the Atlantic. We now need to see action on two fronts: to reduce the number of people affected by dementia in the future, and to minimize its impact on those who do develop the condition.

But this action demands a seismic shift in the way our health systems approach dementia care. This will take time and resources, so health systems and physicians need to be supported to manage this change.

The current state of play

In the past year, we've seen the arrival of the Alzheimer's drug lecanemab (Leqembi) into U.S. healthcare and more recently, in Japan and China. A second Alzheimer's drug, donanemab, is rapidly following suit, and, regulatory decisions from several countries are expected over the coming months.

Although the benefits of these drugs are modest, and with significant side effects for some, it nonetheless marks the arrival of a new wave of treatments that can slow the course of Alzheimer's disease rather than just treating its symptoms. It's a new dawn for dementia, signaling a step-change in the way it will be perceived and diagnosed.

Despite this success, we don't have a straightforward path ahead to rapid, equitable access to these drugs once they are licensed. Work supported by the Davos Alzheimer's Collaborative is highlighting shared challenges while acknowledging country-specific obstacles linked to healthcare infrastructure, demographics, and clinical practices. For many countries, the current state of play is going to make accessing these treatments practically impossible in the short term.

Solving these issues will be impossible without a change in public attitudes and expectations.

Until very recently, a diagnosis of Alzheimer's offered no hope. While receiving a diagnosis is important for the individual and their loved ones to understand what is happening in the brain, make future plans and have the opportunity to participate in research, a lack of effective treatments has left many wondering "what's the point?"

There also remains considerable fear and stigma around dementia. Many people and communities don't understand that dementia reflects physical diseases of the brain, which can be overcome by research. Recent insight work by Alzheimer's Research U.K. suggests that many people struggle to name dementia's effects, with less than 5 percent of people aware that it can cause a loss of body and motor control, stop people from being able to communicate, and create difficulty managing finances. We cannot accept that so many people see dementia as an inevitable part of aging any longer, and improving understanding is vital to ensuring people can benefit

"Our healthcare systems need to be equipped with tests that can not only detect individuals who are in the early stages of Alzheimer's but also those who are at a higher risk of developing the disease."

from new discoveries. Alzheimer's Research U.K.'s Dementia Community Champions initiative aims to do exactly this, by uniting South Asian community members and empowering them to share information locally, reduce stigma, and enhance research representation.

This lack of awareness has also dampened the appetite for innovation. New technologies that could help diagnose dementia have struggled to be adopted into clinical practice. Within the U.K., the National Institute for Health and Care Excellence (NICE) clinical guidelines for dementia are well established, yet the cognitive tests recommended for primary care professionals are quite basic. This discourages the implementation of more innovative cognitive tests that might be more sensitive, offer more insight or be more culturally appropriate.

This means that many people don't get a diagnosis or are simply told they have "dementia," a general term used to describe a set of symptoms, rather than the underlying disease causing the symptoms, such as Alzheimer's or vascular dementia. In England, one in three people living with dementia never receive a diagnosis, and it can take up to four years for someone under 65 to receive a diagnosis of young-onset dementia.

Further compounding this problem is a profound lack of motivation to invest in cutting-edge diagnostic technology from industry, governments, and healthcare systems. Why commit resources to new, expensive tools when, sadly, a historical lack of effective treatments means that a person's Alzheimer's will progress regardless. This has left healthcare systems worldwide grappling with a glaring void in their ability to offer an early and accurate diagnosis.

Currently, the U.K.'s National Health Service (NHS) recommends using lumbar punctures and PET scans to detect and diagnose Alzheimer's. These tools are effective for detecting amyloid—the hallmark protein of Alzheimer's. But it's estimated that only 2 percent of people can currently access such tests because of their limited availability. England has the lowest number of PET and MRI scanners and the second-lowest number of dementia specialists, including neurologists, old-age psychiatrists and geriatricians, per capita among the G7 countries.



That said, these issues are global. The Alzheimer Society of Ontario says that the introduction of a drug like lecanemab could cause diagnostic wait times in the area to skyrocket to seven and a half years, with a lack of specialist staff, biomarker testing, lumbar punctures, and PET scanners making this inevitable. In France, less than 10 percent patients with suspected early-stage Alzheimer's are offered a lumbar puncture, making it difficult to identify the eligible population for these new drugs.

Potential drug-specific challenges also exist. In the donanemab trials, a radioactive agent, flortaucipir, identified tau, another Alzheimer's hallmark protein, in PET scans. Regulators might require a tau-PET scan as part of donanemab's approval. However, while the FDA approved flortaucipir, now being sold by Eli Lilly as Tauvid, it lacks reimbursement in the U.S. and isn't accessible in many countries. It's uncertain whether a test that detects tau in cerebrospinal fluid (CSF) or alternative methods could substitute for tau-PET if donanemab gains approval.

No country possesses adequate diagnostic infrastructure for the potential surge in demand from emerging treatments. We are likely going to see more people coming forward for a diagnosis, at a younger age and with less obvious symptoms, as well as those concerned about their risk of developing dementia in the future. From primary care physicians to specialist dementia services, healthcare systems worldwide must evolve, fostering interdisciplinary collaboration, embracing technology, and cultivating innovation to create new clinical pathways and equip physicians with the skills and infrastructure needed for this changing landscape.

Early diagnosis is key

Drugs like lecanemab and donanemab target and remove the amyloid protein that builds up in the brain as Alzheimer's disease develops and progresses. These drugs work best for people who are in the earliest stages of disease, when they are experiencing mild cognitive impairment, before symptoms have affected their ability to live independently.

For these treatments to reach their full potential, our health systems need to be equipped with sensitive,

scalable and speedy tests that can not only diagnose individuals who are in the early stages of Alzheimer's, but can pinpoint those who are at a higher risk of developing the disease.

Emerging tools and technologies, like digital cognitive tests that are more sensitive, mean physicians can now detect early signs of diseases like Alzheimer's, surpassing traditional pen-and-paper tests. However, healthcare systems like the NHS lag

“The current lack of global diagnostic capacity means health systems are simply not fit for purpose nor for the future of dementia care, and this needs to change.”

in implementing these technologies. With the potential approval of lecanemab in the U.K. soon, the NHS must rapidly increase CSF testing access, from 2,000 to 20,000 annually to meet the specific needs of the U.K. population.

It's crucial to acknowledge that cognitive tests and molecular diagnostics like blood tests must become more inclusive. For instance, cognitive tests conducted in a patient's second language may yield less accurate results, and amyloid levels can vary among different ethnicities or because of common co-morbidities within specific ethnic groups.

While assessing cognitive changes is essential, it's just one part of diagnosing Alzheimer's. Measuring brain amyloid levels, on the other hand, cannot be accomplished through cognitive tests alone; it necessitates a PET scan or CSF sample via lumbar puncture. The current lack of global diagnostic capacity means health systems are simply not fit for purpose nor for the future of dementia care, and this needs to change.

Developing a new clinical pathway

Two decades ago, the field of multiple sclerosis was presented with an opportunity that is similar to what we have today in dementia. MS was once a condition without any effective treatments, but thanks to research, it is now something people can live with while enjoying a good quality of life. This required the development of new pathways, rapid assessment units, and upscaling of multidisciplinary teams and nurse specialists. These changes improved outcomes for all patients, not just those eligible for the specific treatment, and provided the infrastructure to allow for the rapid adoption of new treatments as they became available.

Dementia is now going through the same gear-shift, and thankfully in the next decade we will be seeing a very different picture to today. But action needs to begin now, and this will require concerted efforts from across a broad base of practitioners from primary and community care, as well as sustained investment.

With the arrival of lecanemab already underway in the U.S. and Japan, health systems urgently need to increase access to CSF sampling from lumbar punctures and invest in greater provision of PET scans to determine the eligible patient population for this first wave of new treatments.

Health systems must also be supported to embrace innovation in the form of digital cognitive tests, to be rolled out as triaging assessments in primary care, before those who are identified as at risk are offered more in-depth clinical assessments such as CSF sampling via lumbar puncture or PET scanning.

Against this backdrop, diagnostic blood tests for measuring amyloid and tau levels are advancing rapidly. Some are already in pilot programs in the U.S., Europe, and parts of Scotland. Within the next five years, these tests are expected to become both scalable and more cost-effective than PET scans or lumbar punctures and could be offered to people in local healthcare settings or even as a finger-prick test at home.

Considerable capacity-building is needed for these tests to transition from labs to healthcare settings, including addressing challenges like freezer storage, cold supply chains, staffing, and regulatory approvals. But this requires resources and infrastructure that don't necessarily exist right now.

New tools and techniques also require new training. A survey conducted by Alzheimer's Research U.K. revealed a confidence gap among physicians when using nonroutine diagnostic tests. The results showed greatest access and clinical confidence in the interpretation of MRI scans, while PET scans and CSF tests have the least access and the least confidence in interpretation. This creates a cycle where physicians may hesitate to champion the integration of these novel diagnostics or opt out for their early adoption. To drive change, we must prioritize supporting physicians in adapting their clinical practices.

Strong public messaging is essential alongside these efforts. Different cultures and ethnic groups have varied perspectives on dementia, presenting unique opportunities and challenges for ensuring universal access to diagnosis. Effective public messaging and engagement are crucial for encouraging individuals to recognize Alzheimer's early signs and symptoms and empowering them to seek assessment.

Moving from pilot, to policy, to practice

The journey towards the most recent breakthrough—an anti-amyloid treatment for Alzheimer's disease—has been a long and difficult one. Today, however, we stand at a tipping point in dementia research.

Across the globe, pockets of innovation are propelling us closer to a reality free from the fear, harm and heartbreak of dementia. Initiatives like the Davos Alzheimer's Collaborative Healthcare System Preparedness Learning Laboratory Meetings, which invites experts to share progress with their peers around the globe so that all may benefit from learnings, will serve as invaluable conduits for sharing insights, identifying trends, and fostering a community of best practices as new dementia treatments reach patients.

For the first time, genuine hope permeates the field. While we acknowledge significant challenges and uncertainties, we also see tangible opportunities to begin transforming the lives of those affected by dementia. In the midst of it all, we must seize this chance and ensure that our global healthcare systems are poised to embrace this new era.

Hilary Evans is chief executive of Alzheimer's Research U.K. Professor Sir John Bell is a professor of medicine at the University of Oxford.

The Approaching Alzheimer's Wave

Dementia is on the rise in every region of the world, with vast implications for public health.

By 2050 more than 150 million people worldwide will suffer from some kind of dementia. (Today that number is more like 50 million.) The increase has two major drivers—in some regions, such as sub-Saharan Africa, the wave comes from population growth. In others, such as China and East Asia, dementia is expected to increase as the population ages. But everywhere, researchers write, “growth in the number of individuals living with dementia underscores the need for public-health planning efforts and policy.” The data here track general dementia instead of Alzheimer’s specifically, in part because dementia is more consistently diagnosed worldwide. Here’s where researchers expect the most cases of dementia to emerge. —KP

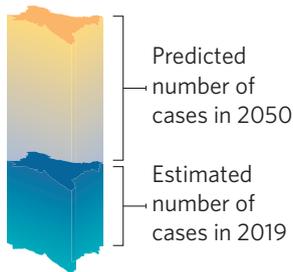
About the data

This map depicts numbers from the Global Burden of Disease study, a comprehensive worldwide effort to quantify the causes of human disability and mortality.

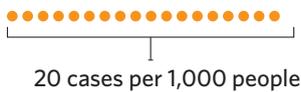
KEY

The global map represents the total number of dementia cases expected worldwide by 2050, broken down by region.

Bar height shows dementia counts in the region.

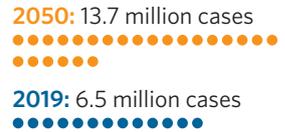


Dots tally the number of cases per 1,000 people—a measure of the disorder’s relative prevalence.

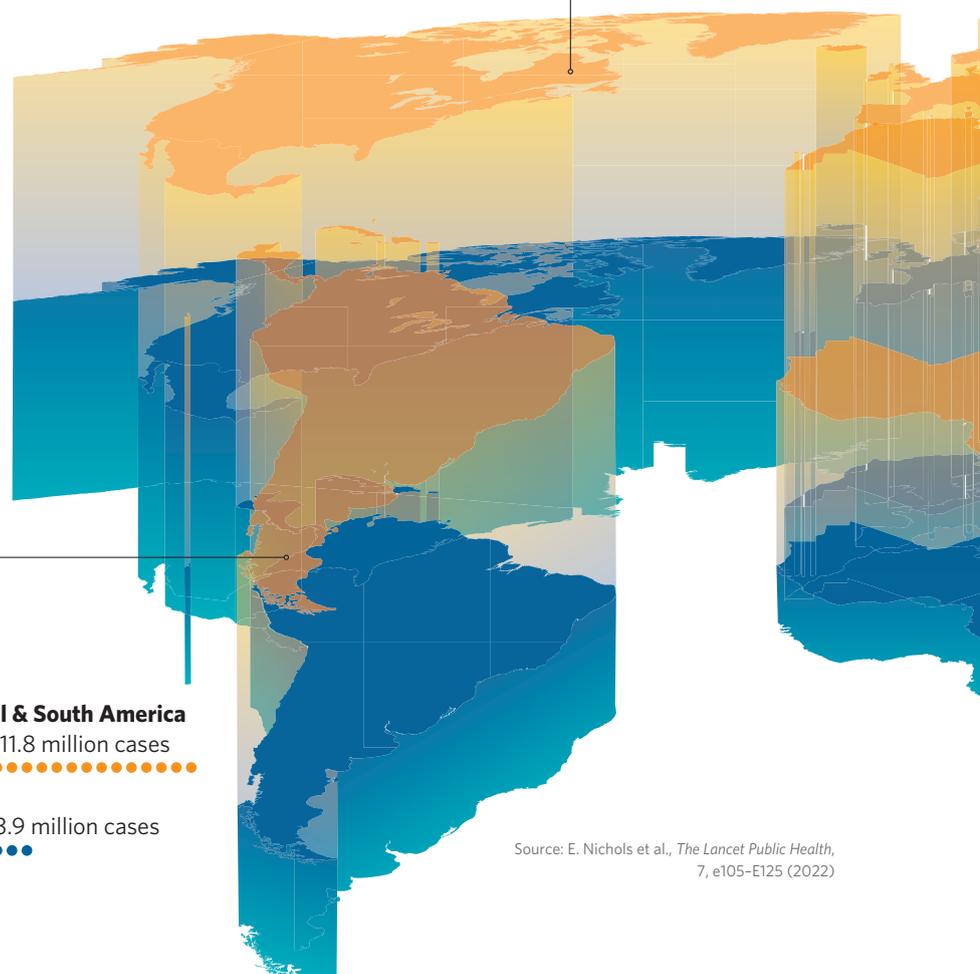


The dementia rate (cases per 1,000 people) also represents the disorder’s burden on the community—in regions with more per-capita dementia, more citizens will need to take on caregiving roles.

North America



Central & South America



Source: E. Nichols et al., *The Lancet Public Health*, 7, e105–E125 (2022)

China and Taiwan

2050: 46.9 million cases



2019: 15.6 million cases



Western Europe

2050: 13.6 million cases



2019: 7.9 million cases



North Africa & Middle East

2050: 13.8 million cases



2019: 3.0 million cases



Northern Eurasia

2050: 10.7 million cases



2019: 5.3 million cases



East Asia

2050: 18.4 million cases



2019: 8.2 million cases



South Asia

2050: 15.1 million cases



2019: 4.9 million cases



Oceania

2050: 1.03 million cases



2019: 0.44 million cases



Sub-Saharan Africa

2050: 7.8 million cases

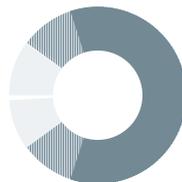


2019: 1.8 million cases

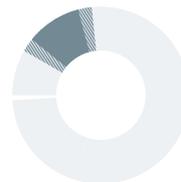


Types of Dementia

Dementia is a disorder that can be caused by several different diseases, most often Alzheimer's. A specific diagnosis can be elusive, especially in places with a less Westernized medical culture. Therefore, worldwide data often track dementia instead, as seen here. Here are dementia's major causes:



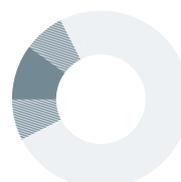
Alzheimer's disease
60-80% of dementia cases



Frontotemporal dementia
10-15% of cases



Vascular dementia
20-30% of cases



Lewy body dementia
10-25% of cases

Source: "Alzheimer's Disease and Other Dementias," Mayo Clinic, 2020.

Lessons from Around the Globe

Community-based programs are exploring new ways of managing Alzheimer's care.



Patrons of the Synval Santos Day Center waiting at the “bus stop.”

arbored patio. There, they sit, chat and reminisce about childhood and the old days, until the panic subsides, as they wait for a bus that never comes.

Years of trial and error have taught Freire's team of 22 caretakers at Synval Santos how to manage sundown syndrome—a pique of late afternoon distress or the sudden urge to flee that is common to Alzheimer's patients. Nimble intervention, one-on-one attention, patience, and a gentle sleight of hand is the routine for the facility's 75 elderly patrons, who have moderate stage Alzheimer's. (At the facility, which is part of the Davos Alzheimer's Collaborative's Healthcare System Preparedness Program, patients come for the day and go home in the evenings.)

“If you show concern, stay calm, and never argue,” Freire told me on a recent visit to the Center, “the stress passes, and even those anxious to flee soon forget their troubles.”

Brazil is a country the size of a continent, with staggering inequalities, where the wealthy enjoy world-class private health services and the poor languish at understaffed public hospitals. Synval Santos Day Center, however, is a rare exception in Latin America: a publicly financed and managed social service that works.

The institution's decade-long record of caring for those with Alzheimer's is already a beacon for Brazil and elsewhere. Its success makes it a magnet for people from surrounding towns and even out of state.

A Gentle Sleight of Hand

The city of Volta Redonda in Brazil has built a model day-care center for Alzheimer's patients.

BY MAC MARGOLIS



On some days, worries can cloud the typically upbeat mood at the Synval Santos Day Center, a modest care facility for the elderly with Alzheimer's disease, in Volta Redonda, the old steel town 60 miles west of Rio de Janeiro. But Danielle Freire knows just what to do.

Freire, a psychologist and the center's coordinator, takes the anguished “patron” (no “patients” here, please!) by the arm and coaxes her (8 of 10 clients are female) to the faux “bus stop” in an

Volta Redonda, however, is atypical. It is one of just 106 towns among Brazil's 5,568 municipalities to provide no-fee services—workshops, exercise and cognitive calisthenics—for the elderly. The city boasts Brazil's first and perhaps its only public center dedicated to Alzheimer's. It's much the same across Latin America, where the number of people with dementia is expected to soar from 7.8 million in 2013 to more than 27 million by 2050.

Many poor nations have islands of excellence in medicine and clinical care, but only for the well-off. Just 25 percent of Brazilians have private health insurance and access to top-tier treatment. In theory, Brazil's Universal Health System (SUS, in Portuguese) tends to the other three-quarters through a nationwide network of free neighborhood clinics and hospitals. The system proved vital during the pandemic, treating COVID emergencies and administering vaccines to mil-

lions, even as the central government downplayed the contagion and dismissed the advice of public-health experts.

But SUS is plagued by chronic underfunding, red tape and patchy services that vary according to the agendas of local officials and national political class.

Volta Redonda was different. A group of forward-looking city officials, social workers and residents in the city were inspired by a local dentist, whose wife struggled for years with Alzheimer's. They saw dementia as a social emergency in the making. In 2015, they launched the Center for the Elderly with Alzheimer's and Family (the formal name for Synval Santos), financed entirely by the city.

In Volta Redonda, where budgets are stretched, creativity helps. Besides the make-believe bus stop, a common tactic in Alzheimer's therapy, the center has developed a strategy of building "workstations" tailored to individual users.

For instance, Synval's staff talk about how rekindling memories helped Zequinha, a former shoemaker (who died in 2022), through some difficult days. "Of course you can go home, but would you mind fixing this shoe first?" a psychologist would ask, coaxing him over to a workbench covered with tools. For Luzia, another patron known for her green thumb, it's the table with potted plants and gardening spades that helps keep her centered. And Luzia and her

"The brunt of the disease burden falls on sons and daughters—especially the daughters. Children often give up their jobs to care for sick relatives. In some homes, the elderly care for the elderly."



Synval Santos's psychologist and coordinator Danielle Freire helps to celebrate Carnival at the day-care center.

friends are soothed by a baby doll which each one is allocated to carry, cradle and rock and call by name, as if their own.

Brazil needs more than artfulness. The country has no national plan or protocols for dementia, and a 2020 bill to launch an Alzheimer's policy is still stuck in Congress. An estimated 80 percent of cases of dementia go undiagnosed, and even when patients test positive, confirmation routinely comes late. "There's a barrier in Brazil to implementing public policy until a problem becomes a crisis," says Felipe Vecchi, a physician and medical director for Brasil Senior Living, a private elderly facility.

One obstacle to prioritizing the elderly in low- and middle-income societies is the host of other endemic problems, including tuberculosis,

yellow fever, HIV/AIDS and dengue—which compete for attention and resources. As a chronic disease, with gradual onset, Alzheimer’s is easy for politicians to ignore or shortchange come budget time. With the share of Brazilians aged 65 and over set to grow 488 percent by 2065, they do so at their peril.

Compounding the crisis is a lack of research on dementia (Latin America accounted for just 6 percent of global clinical trials in 2020) and shortage of resources for screening (there’s a wait period of up to six months for PET scans), which leave patients behind and policymakers with too little data. Families and neighbors become first responders of the dementia epidemic, with knock-on effects across the economy.

“The secondary cost of Alzheimer’s is enormous,” says Otelo Corrêa dos Santos Filho, a psychiatrist in Brazil who works with the Davos Alzheimer’s Collaborative. “The brunt of the disease burden falls on sons and daughters—especially the daughters. Children often give up their jobs to care for sick relatives. In some homes, the elderly care for the elderly.”

As age-related diseases such as Alzheimer’s spread, so will the social fallout. “By failing to make aging and cognitive decline a national priority, we put the welfare of the elderly at risk but also their families and household savings,” says Renato Veras, director of the Open University for Senior Citizens, an annex of the State University of Rio de Janeiro.

Unless planners and policymakers can overcome inertia and acute political short-termism, Brazil’s intrepid family caretakers will need caretakers themselves.

Mac Margolis is a freelance writer based in Rio de Janeiro.



Children in Scotland are being taught how to keep their brains healthy with good exercise and diet habits and an active social life.

Preaching Brain Health to Young and Old Alike

Scotland is putting in place the infrastructure for preventing Alzheimer’s.

BY WILLIAM UNDERHILL



It’s never too early to start maintaining good brain health. That is the message Alzheimer Scotland is sending to children as young as eight, with advice on diet, exercise and keeping up a social life, packaged in online material with eye-catching graphics—and, indirectly, to their parents as well. “The children can be a very good catalyst for conversation in the home and so raise awareness,” says Jim Pearson, the nonprofit’s policy director.

The imaginative approach is typical of Scotland, which increasingly sees itself as a world leader in the field of dementia care, prevention and research. Thirteen years ago, the Scottish government brought out its first national dementia strategy. Since then, it has followed with three more, the latest in 2023. The Brain Health



Scotland initiative, which distributes the brochures to schoolchildren, has the support of the government, prominent academics and Alzheimer Scotland.

In its dementia strategy, Scotland promises every person who has Alzheimer's a minimum of one year's support from a named caregiver after diagnosis. A network of dementia resource centers spans the country. And an Alzheimer's phone helpline has been running since 1989. With an eye to publicity, last year Brain Health Scotland launched a clinic at Murrayfield, the home ground of Scotland's rugby team in Edinburgh, where former players go to get regular brain checkups. The National Health Service (NHS) hopes to set up a chain of similar clinics nationwide by 2025.

About 90,000 people in Scotland have dementia. It is one of the country's leading killers, with a death rate similar to coronary heart disease. Government authorities have come to recognize the role of lifestyle factors in contributing to the disease, as well as the importance of early diagnosis. Together with a new generation of drugs that slow the progress of Alzheimer's, experts reckon that reducing exposure to 12 key risks, such as diabetes or alcohol consumption, can delay or prevent 40 percent of dementia cases.

Researchers have access to a vast pool of anonymized data in the centralized healthcare system of the NHS. Scotland can also lay claim to its own particular tradition of medical record-keeping. As far back as the 1930s, it launched a unique survey testing the intelligence of the nation's children. The performance of almost all those born in 1921—more 80,000 in total—was logged, creating a useful reference resource for population studies.

The spirit of cooperation among the main stakeholders is crucial. For instance, the University of St Andrew's, the country's oldest university and the alma mater of Prince William, has twice in the last two years hosted international brain-health summits, bringing together leading figures from what's called the "triple helix" of universities, healthcare providers and the commercial life sciences sector. "What is unique in Scotland is the level of collaboration," says Pearson.

Such joint efforts hold out the promise of commercial dividends. Frank Gunn-Moore, an expert in neurodegeneration at St An-

"Early diagnosis will be transformative in the way we assess, manage and conceptualize clinically Alzheimer's disease."

drew's—whose recent work on the brains of stranded dolphins made headlines by revealing that their brains showed some of the classic markers of human Alzheimer's—is seeking to create a government-backed fund that would help form spin-out companies from all Scottish universities working on Alzheimer's and dementia. "Drug companies really want to work in Scotland because it's manageable," says Gunn-Moore. "We are ambitious: we really want to go big scale."

It's happening already. Earlier this year the healthcare giant Roche Diagnostics announced a partnership with Scottish Brain Sciences (SBS), an Edinburgh-based research institute, to ex-

plore the earliest biological signs of neurodegenerative disease using blood-based biomarkers. "Early diagnosis will be transformative in the way we assess, manage and conceptualize clinically Alzheimer's disease," says Craig Ritchie, the firm's founder and CEO, who has emerged as a central figure in the world of Alzheimer's research and prevention. The selection of SBS for the project was a "huge vote of confidence in the Scottish life sciences sector."

Disillusioned by the bureaucracy of the NHS and the lengthy delays facing patients waiting for appointments at memory clinics, SBS is now rolling out its own network of dementia-prevention research centers across Scotland. On offer will be free access to the latest diagnostic tests and medication through big drug trials funded by the pharmaceutical industry. In Ritchie's words: "We are ready for this next generation of treatments to start. The problem is the infrastructure is not in place to do it."

Scotland is one of six countries participating in a pilot program, funded by the Davos Alzheimer's Collaborative, that is making new blood tests and digital cognitive assessments available to Alzheimer's patients. "We have a proud history of being at the forefront of dementia policy, of being half a step ahead of others, so it follows naturally that there's interest in research," says Wendy Chambers, a dementia consultant working on the trials.

Who knows where that will ultimately lead? Chambers says: "It might not change much for my generation, but it certainly starts to change what the progression of the disease looks like for future generations."

William Underhill is a freelance writer based in Oxford, U.K.



It Takes a Village

Community leaders in Kenya are increasing awareness of Alzheimer's and reducing the stigma.

BY APRIL REESE

A few years ago, mental health researcher Christine Musyimi traveled to rural Kenyan villages to investigate how people perceived dementia. She made some disconcerting discoveries. Some people thought that dementia was simply part of the aging process. Others had never heard of Alzheimer's or thought it was strictly a Western disease. Still others thought people showing symptoms of dementia were cursed and were being punished by the gods.

Today it's another story. "We've come from very far," says Elizabeth Mutunga, a psychotherapist who founded Alzheimer's and Dementia Organization Kenya (ADOK), a Nairobi-based nonprofit advocacy and research group, and has worked to educate people about dementia. "It took a lot of knocking on doors, but now

people are no longer pushing it under the rug and saying, 'there's nothing we can do about it,'" says Mutunga, who was a coauthor, with Musyimi, of a 2021 study reporting the work. "There's a better understanding of the condition now."

An estimated 87,000 people in Kenya have some type of dementia. By 2050, the number of cases is projected to rise to 361,000—a 315 percent increase—driven primarily by population growth. But before ADOK's work, misperceptions about dementia have kept many people in Kenya, a largely rural nation of 55 million people, from getting the care that they need.

"The combination of poor awareness and ill-equipped health-care systems leads to stigma manifested in the form of patchy diagnostic pathways, neglect and abuse," Musyimi, Mutunga and their co-authors wrote in their 2021 study.

To combat misperceptions about Alzheimer's, in 2022 ADOK, the Kenya Ministry of Health and others teamed up to create the STRIDE Kenya initiative. (STRIDE stands for Strengthening Responses to Dementia in Low and Middle Income Countries.) Based on input from dementia patients and their caregivers, the idea is to get more people talking about Alzheimer's disease. "We know the most effective way to reduce stigma is through social contact," says Sara Evans-Lacko, a mental health services researcher at the London School of Economics and Political Science who worked on an anti-stigma toolkit the STRIDE Kenya team developed.

The toolkit, called "Don't Forget I'm Human," includes an intervention how-to for caregivers and clinicians. The centerpiece of the approach is to gather caregivers, show them videos of people with dementia, and then hold a discus-





Building trust among caregivers is an important part of nonprofit ADOK's approach in Kenya.

“We’ve come from very far. It took a lot of knocking on doors, but now people are no longer pushing [Alzheimer’s] under the rug and saying, ‘there’s nothing we can do about it.’ There’s a better understanding of the condition now.”

sion in which caregivers share their thoughts and personal experiences. Participants are encouraged to reflect on how they can support the people with dementia they are helping take care of. “It’s really trying to humanize people with dementia, to build empathy,” says Evans-Lacko.

Building trust among caregivers is an important component of the approach. “We didn’t want to just go in and start telling them about dementia,” says David Ndeti, a professor of psychiatry

at the University of Nairobi who helped design the intervention. “We went right to the families, and we asked them a simple question: Do you see people who seem to forget sometimes?” That started a dialogue based on mutual respect, he says.

The next step after education is to find ways of delivering care. To that end, Musyimi spearheaded the DEM-SKY project, an initiative to train community healthcare workers in rural Makueni County in screening people over 60 for de-

mentia at the same time as other conditions, such as diabetes. The project, which is funded by the Davos Alzheimer’s Collaborative (DAC) and is the first of its kind in Kenya, screened 3,500 people in rural areas for six months. It found dementia in about 18 percent of cases.

The team is now trying to secure funding to determine whether the trainings led to increased access to care. Mutunga believes they’ll find that it has. “Once people have understanding, then a lot of people actually come in to get care,” she says.

The challenge now is to scale up these efforts and make screening, care and support the norm and not the exception. Kenya’s Minister of Health Simon Njugu-na told a June 21 virtual meeting on healthcare system preparedness, convened by DAC: “We’re very keen to develop a national plan on dementia.”

So far, Alzheimer’s advocates have made “great progress in terms of the policy impact,” says Evans-Lacko. “So don’t give up,” Mutunga says. “Keep pushing. Eventually the door will open.”

April Reese is a freelance writer based in Aveiro, Portugal.



Teaching Good Brain Hygiene

In Japan, where more than 90,000 people are 100 years or older, clinicians are advocating lifestyle habits that reduce the risk of Alzheimer's.

BY MIHOKO IIDA

Hisatomo Kowa is not waiting around for new drug treatments for Alzheimer's. He is already exploring preventive measures, including changing fundamental lifestyle habits before the onset of the debilitating disease.

"Once a patient is diagnosed with the disease, there are drugs to treat the symptoms. But the disease itself cannot be cured," says Kowa, a neurologist and director of the Dementia Preventing Center at Kobe University Graduate School of Health Sciences. "So how can we prevent or delay the onset at an earlier stage?"

Since 2019, Kowa has been leading a program, called Cognicare, at Kobe University. It emphasizes the importance of educating the public on leading a balanced lifestyle that cares for and boosts brain function, including healthy eating habits and exercises that mix mental tasks with physical ones. "If we are all living to be 100

years old, we should all be more mindful of brain health from an early age," he says.

Kowa's view reflects a common societal attitude towards aging and mental health in Japan, which currently has one of the oldest populations in the world. In 2021, the average lifespans were 81.5 years for men and 87.6 years for women, according to government statistics. With many people living to well over 100—Japan had more than 90,000 centenarians in 2022—the number of people being diagnosed with Alzheimer's disease and other forms of dementia is on the rise. The Health Ministry estimates approximately 7 million will be diagnosed with dementia in 2025, up from 4.62 million in 2012. "People need to change their lifestyle habits beginning in their 40s because the brain begins to change roughly 20 years before the onset of dementia," he says.

Cognicare aims to teach people good brain hygiene. For the equivalent of \$40 per month, each

Gerontology, based in Aichi Prefecture, instructors and caregivers proselytize on social media platforms, including Instagram and YouTube, where they demonstrate fun and creative ways to stimulate the brain while exercising, including word games, counting backwards while walking and clapping your hands while stomping your feet. The exercises often focus on focusing the mind on one task while the body performs another. The goal is not to get better at both tasks but rather to tax the brain and the body simultaneously.

"The exercises are actually complex and difficult to do," says Mie Nishihama, a caregiver and occupational therapist at Shigei Hospital in Okayama Prefecture, who has been overseeing classes offered by the hospital's culture and fitness arm, Harmony Kurashiki, since 2019. "But what's important is for the exercises to be done in groups so that participants have people to laugh with when they make mistakes."

"We are all at risk of dementia as we age. And there is no single answer to prevent this. It's not just about nutrition, or exercise, but it's about leading a balanced lifestyle starting early and continuing for as long as possible."

participant gets a basic medical checkup; attends health-related seminars, including information on nutrition; and takes part in "cognicise" exercise classes (available physically or over video-conferencing). The program has attracted participants from 40 to 90 years old, with most in their 70s.

Cognicare has garnered much media attention. Created by the National Center for Geriatrics and

She stresses the importance of a communal connection, especially among the elderly. The program does not collect data on how much patients improve from the exercises.

Yuka Ota, a certified instructor of cognicise in Shizuoka Prefecture, says that teaching elderly people is "similar to running up a down escalator." She has been teaching classes at various facili-

ties since 2016. Her impression is that while it is hard to see her students making significant improvements, she knows from experience that “sustaining the status quo [in health and cognition] takes a tremendous amount of effort.”

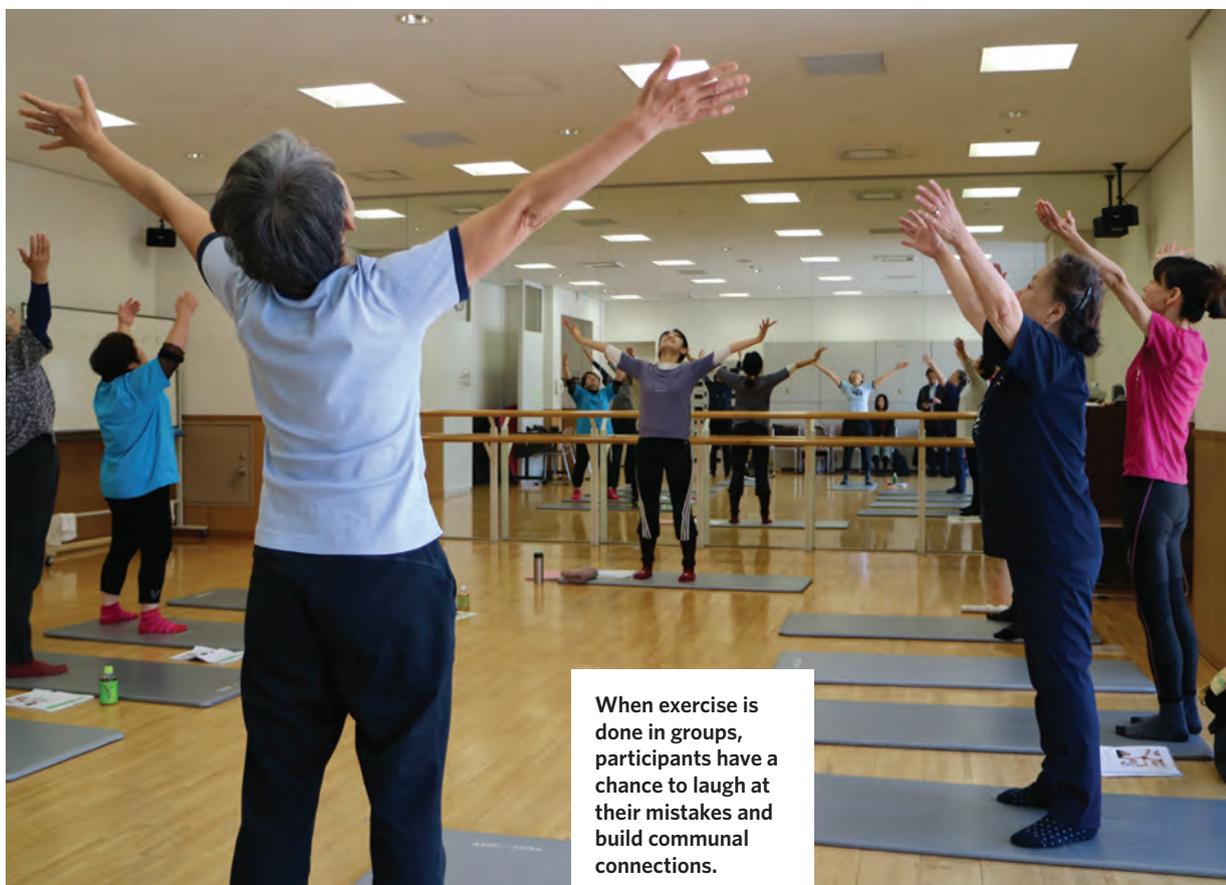
Kowa is currently working on the final analysis of the effects of

Preparedness Program. He hopes the study’s results will contribute to the development of dementia-prevention measures in Japan.

To better educate the public on brain health, Kowa also recently published a nutrition book for a general audience. The title translates from the Japanese roughly as: “Eighty is not too late to start.

cognitive, and physical activity) may prevent or delay up to 40 percent of dementia.

“Alzheimer’s disease is not something that happens suddenly. This is why it’s important to have a comprehensive program such as Cognicare to check for early signs so that medical professionals can better guide patients to minimize



When exercise is done in groups, participants have a chance to laugh at their mistakes and build communal connections.

a separate multifactorial intervention aimed at preventing dementia. Specifically, he and his group are exploring the significance of two new methods for the early detection of Alzheimer’s disease: a digital cognitive assessment tool, and a tool to estimate the presence of amyloid in the brain using blood-based biomarkers, as part of the Davos Alzheimer’s Collaborative Healthcare System

How to eat to keep dementia away: The complete guide.” The book introduces foods, such as some types of fish, that are good for the brain and warns against lack of sleep, as well as smoking. He also cites in the book the 2020 report of the Lancet Commission on Dementia Prevention, Intervention, and Care that states modifying 12 risk factors (including the lack of education, nutrition, and social,

the deterioration as much as possible,” says Kowa. “We are all at risk of dementia as we age. And there is no single answer to prevent this. It’s not just about nutrition or exercise, but it’s about leading a balanced lifestyle starting early and continuing that lifestyle for as long as possible.”

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Taking It to the Streets

In Armenia, clinicians travel the countryside in a minivan, offering tests for Alzheimer's.

BY APRIL REESE

Arax Vartevanian started forgetting names and dates in 2017, but she wasn't diagnosed with Alzheimer's until last year, when a neurologist ordered a brain scan and blood test. By then, she had developed a tendency to repeat a question over and over. Her husband, Gegham, grew increasingly frustrated trying to get her to stop, to no avail.

Recently, though, Gegham learned a crucial piece of information that helped him cope with his wife's illness: "Repeating stories or asking questions over and over again are symptoms of [Alzheimer's] disease and are not intentional," he read in a guide for caregivers. Now, he says, when the same thing happens, he usually gives in.

Helpful advice for Alzheimer's caregivers has not been commonplace in Armenia. The former Soviet republic, with a population of 2.8 million at the crossroads of Europe and Asia, has largely neglected its dementia patients, because of a lack of awareness of the condition and stigma. But the country has made considerable progress, in part because of the work of NGOs such as Alzheimer's Care Armenia (ACA),

which in 2021 began distributing 10,000 caregiver's guides to clinicians and patients—the guide that proved so helpful to the Vartevanians. The ACA, with funding from the Davos Alzheimer's Collaborative (DAC) and other organizations, has put in place several initiatives designed to bring medical and psychological support to Alzheimer's patients.

Jane Mahakian, a gerontologist who lives in the U.S., founded ACA in 2017 after she noticed, during her decades of trips to Armenia, that many people lacked an awareness of Alzheimer's. She organized the country's first Alzheimer's conference in 2018, and, to her surprise, more than 400 people attended. "That was a pivotal point in our efforts to start creating visibility and just get people to start thinking about cognitive impairments not only for older adults but for all adults," she says.

Building on that momentum, she collaborated with Mission Armenia, an NGO that provides meals and other support to the elderly, to establish two "healthy aging memory clubs," where people with mild to moderate memory challenges can engage in activities that promote brain health, such as playing games, socializing, and making music and art. At these clubs, held at the Mission Armenia facility in Yerevan, psychologists lead movement therapy sessions, give classes on education and nutrition, and conduct tests every three months to track participants' cognitive abilities. "Those small programs were actually very instrumental in building up the awareness and visibility within the country," she says. (Two other NGOs, Mission Armenia and Oron, now oversee the groups.)

Participants are tested every three months to track changes in cognition. "We have seen people

score better on their assessment test" after participating in the programs, she says.

For people with more advanced dementia, ACA started



a memory cafe in October 2022. Weekly gatherings, led by a psychologist and a social worker, offer a safe space for people with dementia to engage in cognitive exercises and games over coffee and snacks and for caregivers to get support. "It's a happy place for them," says Mahakian. "It's a way to connect. For many of them, this is really the only place where they feel a sense of belonging."

To reach more people who may need Alzheimer's care, Mahakian got the idea to create a mobile clinic in a minivan that would travel the country with a team of clinicians. She partnered with Armenian EyeCare Project, a mobile clinic for eye care that had already

been conducting exams and performing surgeries. Beginning in June 2022, ACA's healthcare providers have been following the EyeCare vans and providing de-

that runs the mobile screening unit, also provides training to healthcare providers at hospitals and clinics around the country in recognizing signs of dementia.

lation of researchers is working to strengthen dementia research capacity. Under a new project called COBRAIN Armenia, Yerevan State Medical University, with input from advisors from across Europe and the U.S., is exploring new ways to treat and prevent chronic brain disorders, including Alzheimer's disease.

Zaven Khachaturian, president of the Campaign to Prevent Alzheimer's Disease, who serves as an advisor on the project, says it could play an important role in improving care for people with not just dementia, but other brain disorders as well. "It would benefit not only Armenia, but it would be a prototype for building a next-generation healthcare system for chronic brain disorders," he says. Khachaturian is Armenian, but lives in the U.S., and served as associate director at the U.S. National Institute on Aging from 1977 to 1995.

In March, as part of a wider World Health Organization initiative, Armenia began drafting a national dementia plan. Although details haven't been released, Mahakian would like to see the government mandate screening for dementia by physicians during annual checkups.

Key to improving care, she says, is strengthening coordination between NGOs, researchers and the Armenian government. "We're really working on developing these multilevel partnerships to not only create sustainability for our early detection screening program that we have been very successful with but also to develop better ways to get people care," she says. "How do we best meet their needs and treat them? We really need to think outside the box."

April Reese is a freelance writer based in Aveiro, Portugal.

Activities such as crafts, games and music promote healthy brains. Below: a memory cafe run by Alzheimer's Care Armenia.



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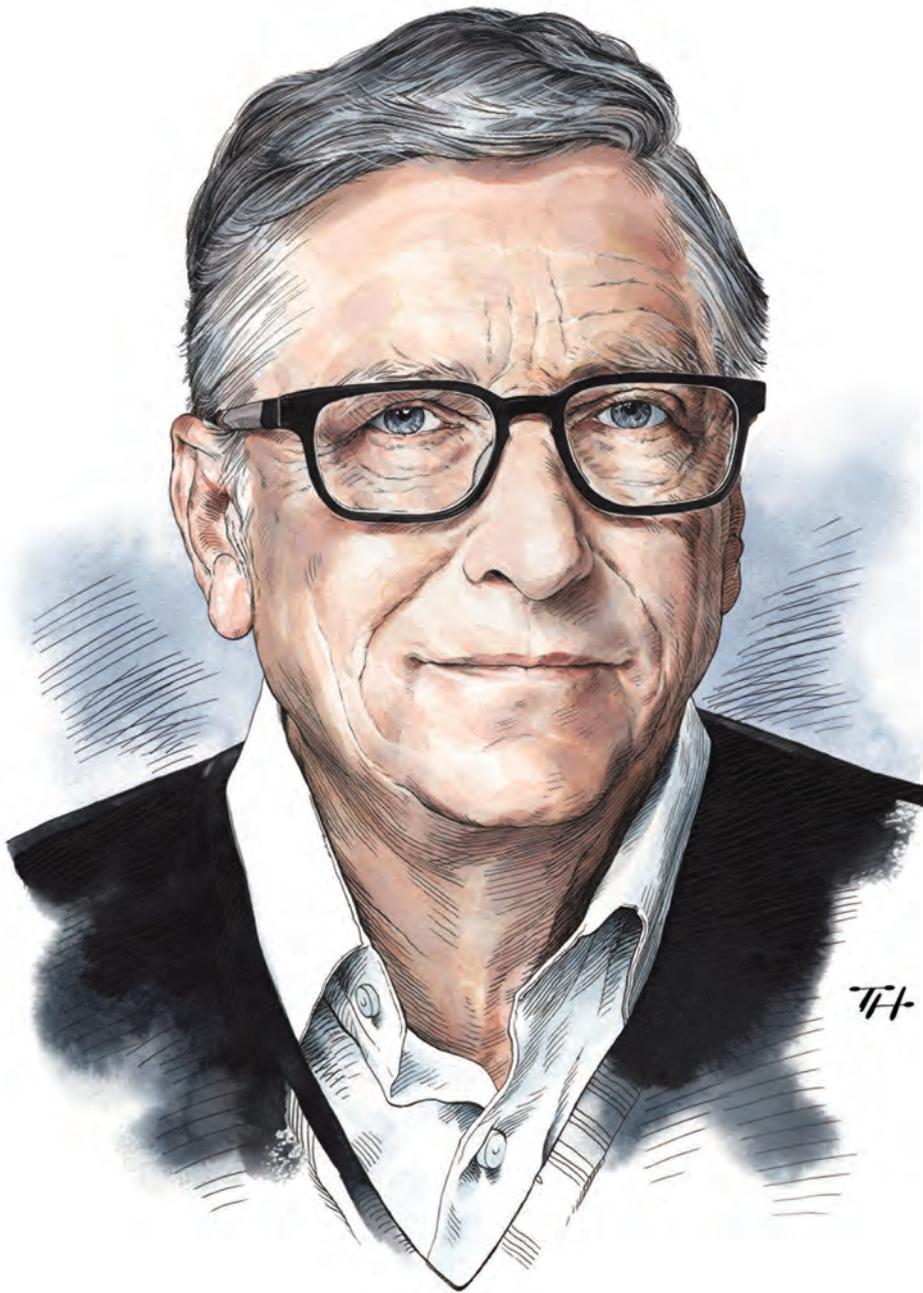
mentia screening to their clients. "Partnering with them was very important" for getting buy-in from both patients and healthcare practitioners, she says. "It took the fear out of the disease."

The Brain Health Armenia Project, a DAC-funded program

In May 2023, the project began providing in-home care to Alzheimer's patients as well.

ACA has also tried some unconventional strategies for spreading awareness and improving care. The organization teamed up with a robotics expert, Karen Khachikyan, to develop "Robin the Robot," a dementia companion deployed at the Nork Old Age Home in Yerevan. Studies found that Robin the Robot helped alleviate loneliness and isolation and improve cognitive ability of the residents. ACA also started a national radio show on the country's public radio network to showcase "older adults leading positive lives," says Mahakian.

A small but ambitious constel-



“We’re at a tipping point with Alzheimer’s”

Bill Gates talks about his own experience as a caregiver and what needs to be done to fight this disease.

It would be hard to imagine any one person who’s had more of an impact on public health than Bill Gates. Much of the wealth he amassed as founder of Microsoft has gone to charity—according to *Fortune*, he is one of only five billionaires to have given away more than 20 percent of his wealth. In 2023, the Bill and Melinda Gates Foundation, which he started with his former wife, Melinda Gates, spent more than \$8 billion of its more than \$70-billion endowment.

Gates has focused his philanthropy largely on some of the most intractable health problems, such as malaria, HIV/AIDS and childhood vaccination. In recent years, he has turned to Alzheimer’s disease, starting with diagnostics and more recently expanding to proteomics and healthcare programs related to the disease. Scientific American Custom Media asked him about Alzheimer’s:

SCIENTIFIC AMERICAN CUSTOM MEDIA:

What sparked your interest in Alzheimer’s? How has your personal experience with the disease contributed to your decision to get involved?

GATES: Like many people, I have a personal connection to Alzheimer’s. My dad died from Alzheimer’s, so I understand first-hand what a cruel disease it is, and how difficult it can be to watch a loved one suffer with it. We were fortunate to have the resources to provide my dad with excellent care, and our

If we're able to catch the disease sooner, we'll be able to give patients more options for treatment, social services and participating in clinical trials.

family is grateful for the wonderful caregivers who helped him in the 13 years he lived with the disease. But for the majority of families battling Alzheimer's, this is not an option. Caregiving most often falls to a spouse or a child, which can be overwhelming.

The financial burden of the disease is easier to quantify than the emotional cost. The lifetime cost of care for Alzheimer's and other dementias is rapidly increasing in the U.S., Japan, Europe, and other countries. According to the Institute for Health Metrics and Evaluation, the global cost will exceed \$1.6 trillion by 2050 and represent nearly one-third of all healthcare spending. Unlike those with many chronic diseases, people with Alzheimer's incur long-term care costs as well as direct medical expenses. If you get the disease in your 60s or 70s, you might require expensive care for decades.

As I spent time learning about Alzheimer's and the research into it, I came to understand the challenges. The brain can't be sampled easily or often, for example, and the blood-brain barrier is a double-edged sword—it both protects the brain and makes it harder for treatments to get in.

Even so, as I learned about all the innovation in this field, I grew optimistic about the ability to make progress toward treatment and eventually a cure. This is a frontier where we can dramatically improve human life. It's a miracle that people are living so much longer today, but longer life expectancies alone are not enough. People should be able to enjoy their later years—and

we need a breakthrough in Alzheimer's to fulfill that.

As someone who takes a bird's-eye view of major health issues, how would you describe the current outlook for Alzheimer's research and clinical practice?

After decades of negative clinical trials and dozens of failed therapies, researchers are making progress on both diagnostics and therapeutics.

Blood-based diagnostics are advancing rapidly—the first blood test for Alzheimer's, PrecivityAD, was launched in late 2020. A few

The therapeutic pipeline is diverse and robust.

others have followed since, but we are looking forward to the first FDA-cleared blood tests on the horizon. Once this becomes a reality, the next hurdle will be ensuring these tests are used properly, accessible and available to the patients that need them, and that we understand how these tests work in different patient populations.

The therapeutic pipeline is diverse and robust—at the beginning of 2023, there were 187 trials assessing 141 different therapeutics. The anti-amyloid agent lecanemab has been approved for use in patients, and donanemab is expected to follow soon. Other therapeutics in the pipeline include

disease-modifying therapies and cover a wide range of approaches, including amyloid and tau but also newer mechanisms such as neuroinflammation, synaptic plasticity/neuroprotection, metabolism and oxidative stress (see J. Cummings et al., *Alzheimers Dement* (N Y), Apr-Jun 2023, Vol. 9: e12385).

With these and other breakthroughs that are coming, it's fair to say we're at a tipping point on Alzheimer's.

In recent years you've directed funding to accelerate development of diagnostic technologies for Alzheimer's. Why did you pick that particular area to start?

We systematically looked at the barriers to R&D on Alzheimer's disease, and we heard consistently that not having a simple, non-invasive, scalable and relatively inexpensive diagnostic (such as a blood test) was a key challenge. It's a barrier to early diagnosis and subsequent enrollment in clinical trials—and continuing to make advances on the disease depends on getting enough people enrolled early enough in trials.

Another problem is that the commercial market for diagnostics does not stimulate investment, so potential scientific breakthroughs are not being pushed forward as rapidly as they should be. This is why I partnered with the Alzheimer's Drug Discovery Foundation to create the Diagnostics Accelerator, which is designed to advance bold ideas for easier, more accurate and earlier diagnosis of Alzheimer's disease.

Do you have any plans to direct funding to accelerate progress in other areas of Alzheimer's, such as treatments, diversity in clinical trials, public-health outreach or others?

We're focused on five areas: understanding the biology of the disease, diagnosing it, treating it, overcoming bottlenecks in clinical trials, and making it easier for researchers to share data with each other.

One of our latest investments is with the Global Neurodegeneration Proteomics Consortium, which brings together data from more than 40,000 blood samples around the world so researchers can identify biomarkers for detecting neurodegenerative diseases and identifying new mechanisms to test. We're also partners in the Clinical Trial Recruitment Lab and the Global Alzheimer's Platform Bio-Hermes Study, both of which are aimed at recruiting people from diverse backgrounds to join clinical trials.

We're also partnering in the Davos Alzheimer's Collaborative's Healthcare System Preparedness Initiative, as well as a recently announced Innovative Health Initiative-funded program, AD-RIDDLE, all of which are efforts to ensure that breakthroughs can be deployed in healthcare systems once they're approved for use.

You've written about how data sharing is vital to learning more about Alzheimer's disease and accelerating progress. Why is that so important and how is that effort going?

Over the past few decades, drug trials and longitudinal cohort studies have generated an enormous amount of data. But right now, that information is not being

shared to the fullest extent possible. Much of it remains locked away or accessible only to select groups. That's a missed opportunity as well as a disservice to the people who agreed to join studies so they could help advance the field.

To help unlock these datasets while making sure they're used responsibly, we worked with several partners to launch the Alzheimer's Disease Data Initiative. Our goal is to help researchers from around the world access more informa-

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tion by making data and data platforms interoperable. So far, the effort has established interoperability with several data platforms, including the Dementias Platform U.K. portal, the Vivli Platform, and the Global Alzheimer's Association Interactive Network platform (GAAIN).

More recently we've gotten involved in the European Platform for Neurodegenerative Diseases (EPND), which is building a platform that will help researchers make their data and biosamples shareable. Their platform will build on data and analysis tools made available by the Alzheimer's Disease Data Initiative, including the Global Research and Imaging Platform, a nonprofit that I fund. Finally, we've created a two-year fellowship, named after my dad, that brings in researchers from

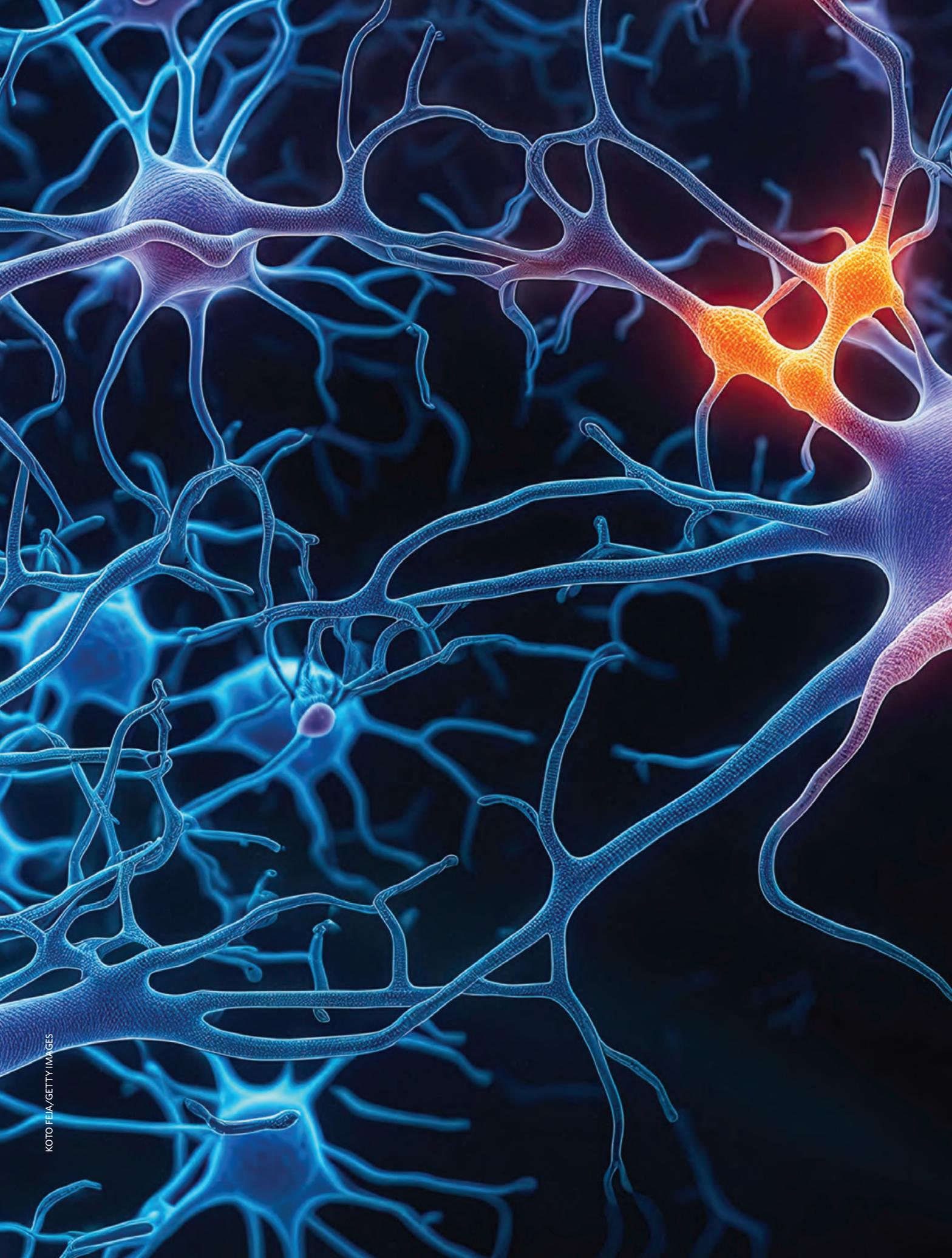
around the world to work on data analysis and to champion the idea of interoperability.

What is the biggest obstacle to making progress on Alzheimer's? Is there a cultural shift that needs to happen?

Although we've recently seen important advances in therapeutics and diagnostics, there is still a lot we don't know about Alzheimer's disease and the brain. Timely diagnosis is the first major shift that needs to happen—many studies have shown that Alzheimer's disease and dementia are dramatically underdiagnosed today. If we're able to catch the disease sooner, we'll be able to give patients more options for treatment, social services, and participating in clinical trials and other research opportunities.

But Alzheimer's disease is also a heterogeneous disease, and patients who have it show a wide range of pathologies in the brain and resulting symptoms. I'm hopeful that the field will be able to capitalize on recent advances in diagnosis and treatment—and also make it easier and more efficient for people to enroll in Alzheimer's clinical trials—so we can continue to improve our understanding of subtypes of the disease and target our efforts at treatment and prevention.

Finally, there is still a lot of stigma surrounding neurodegenerative diseases. That makes it harder to discuss them openly. But I think a lot of that is driven by the fact that these diseases seem so mysterious because we haven't had sophisticated diagnostics or treatments. I'm optimistic that as more advances happen, the stigma will fade, and open public conversations about Alzheimer's will accelerate progress even more. ■





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