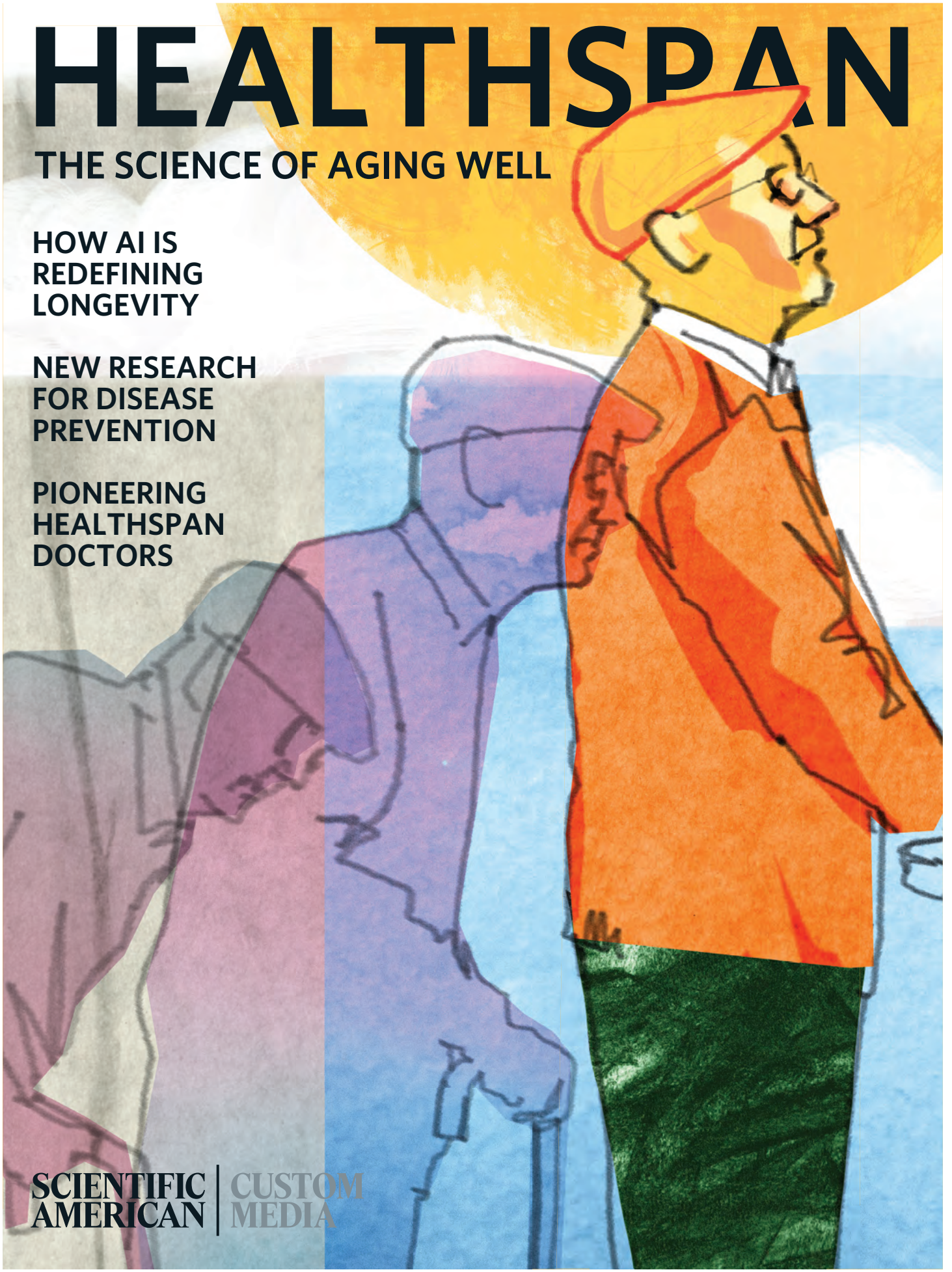
HEALTHSPAN

THE SCIENCE OF AGING WELL

HOW AI IS REDEFINING LONGEVITY

NEW RESEARCH FOR DISEASE PREVENTION

PIONEERING HEALTHSPAN DOCTORS



SCIENTIFIC AMERICAN | CUSTOM MEDIA

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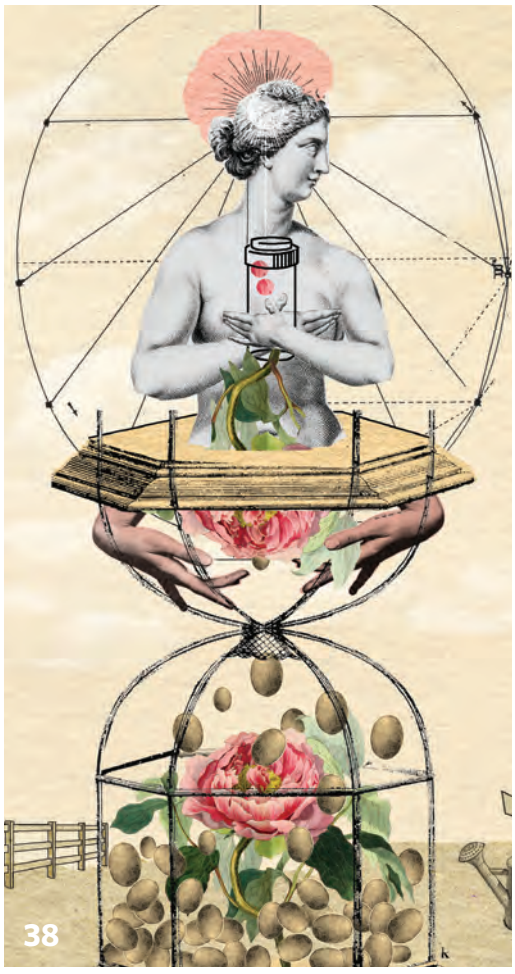

on the cover:
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SCIENTIFIC AMERICAN

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The Age of Aging Better

BY JEREMY A. ABBATE

My maternal grandmother, Georgianna, was just two years shy of becoming a centenarian when she passed away peacefully in 2014, in the comfort of her daughter's (my mother's) home. Born to Italian immigrants in New Haven, Conn., where she would spend most of her 98 years, she found purpose in her work as an expert seamstress in her brother-in-law's bridal gown shop, in meaningful socializing with friends and family, and in cooking. Among many specialties was a most treasured dish for guests: homemade cavatelli (to this day my absolute favorite pasta).

She was also a life-saving force for her husband, Raphael (Ralph), my grandfather, through the many age-related complications of his Type 2 diabetes: neuropathy (nerve damage, especially in the feet); diabetic retinopathy (eye and vision problems); renopathy (kidney disorder); and, what ultimately proved fatal for him, cardiovascular disease.

Despite facing many challenges from this complex chronic illness, my grandmother saw to it that he stayed as healthy as possible. She administered his daily insulin injections, oversaw his exercise regimen, and watched his diet like a hawk (allowing him just the right portion

DAN BEJAR

size of that delicious cavatelli, with plenty of accompanying vegetables and protein). He died just before his 83rd birthday.

Their story is, in many ways, emblematic of the paradox of longevity: medical innovation (such as the discovery of therapeutic insulin and antibiotics) along with centuries of public health successes (clean water, the control of infectious disease, safer food, global vaccine dissemination) have given humans increasingly longer lifespans. With those prolonged lives come, for many of us, the debilitating diseases of aging: cancer, diabetes, neurological conditions like Alzheimer's and Parkinson's, arthritis and other inflammatory conditions, obesity, kidney disease and many others.

While my grandfather's *lifespan* was no doubt protracted by a confluence of scientific advancements (and the loving tenacity of his spouse), he did not enjoy the *healthspan* my grandmother was afforded: her many years of productive living, relatively disease-free.

This concept of healthspan—the years of life that remain free of serious disease—has attracted considerable attention lately in popular media and among scientists engaged in longevity research. It is regularly discussed among all the major stakeholders of life science and is the North Star for much of the research in biotechnology, data science and AI, wellness, nutrition, mental health and other disciplines aimed at tackling age-related disease. It is also a catalyst for renewed conversations among policymakers, economists, sociologists and those tracking the demographic shifts of our global aging population. According to recent projections from the U.S. Census Bureau, the number of Americans who are 100 and older is projected to more than quadruple over the next three decades, from an estimated 101,000 in 2024 to about 422,000 in 2054.

It is high time we take healthspan seriously and follow the exciting science that is developing therapeutics to treat, and potentially prevent, the onset and progression of multiple age-related conditions. A healthier, happier and more productive wave of older people will no doubt reshape the world in tremendous ways, and the implications are profound for many facets of society.

A healthier, happier and more productive wave of older people will no doubt reshape the world in tremendous ways.

Of course, any thorough and evidence-based exploration of this topic must also call out some of the very unscientific concepts, notions and misinformation hindering our true understanding of healthy longevity.

I am thus thrilled to introduce *Healthspan: The Science of Aging Well,* an exciting new collaboration from Scientific American Custom Media and a coterie of vested supporting partners, including Google, Phenome Health, The Buck Institute for Research on Aging, and Optispan. This special edition and media program explores in depth the next wave of innovation poised to give humanity more productive life years, and it separates fact from fiction, hype from hope. We have contributions from such noted experts as Lee Hood, Scott Penberthy, Matt Kaeberlein, Francesca Duncan and Morgan Levine. Many of the contributors and researchers involved in this project were motivated in part by family members or loved ones whose lives were cut short by disease or made more challenging by the vicissitudes of old age. We are honored to showcase their passion for the topic and their vision for a healthier world.

Just as the factors driving longer lifespans were diverse and multidisciplinary (better informed individual lifestyle choices, new therapies, preventive medicine, policies supporting public health), so will be the solutions for longer healthspans. They will no doubt include debates on how funding priorities should be organized and what research should be supported, but they will also include philosophical questions such as "What makes for a purposeful, productive or happy existence?" We welcome such dialogue and hope that it sparks interest from an array of health-interested audiences from all parts of the world.

The desire for better health, for ourselves and for our loved ones, is a powerful unifying force in a world that in so many ways remains divided. Good health is a gift. We can all be champions of the science and policy that drive it forward, so we can each live as productively and meaningfully for as long as we can, and in our own way.

After all, for some, life is a bowl of cherries; for others, a bowl of delectable homemade cavatelli.

***Jeremy A. Abbate is the publisher of* Scientific American.**

The Healthspan Paradigm

People are living longer than ever, but often with chronic disease. Scientists are finding new ways to slow aging and deliver lifelong robust health

BY DAVID H. FREEDMAN | ILLUSTRATIONS BY GREG BETZA

Good news for worms: Researchers have found a treatment that extends roundworms' lives by up to a factor of ten. They've also learned how to give mice an extra 50 percent of healthy longevity. And a healthy-life-extending treatment is now being tested on dogs whose owners are eager to keep their beloved pets around as long as possible.

But what about us? Can medical science help more people—perhaps even most—live past 90 and longer in good health?

Science may be closer to delaying the various infirmities of aging than most people realize. Drugs known to slow aging in animals might well safely do the same for humans, and researchers are working hard to bring more of them closer to clinical trials. One of them, metformin, has already been approved by the FDA for testing as an anti-aging drug, and others are being taken by hundreds of people outside official trials. "I've been in this field for more than 30 years, and I've never seen this level of excitement," says Steve Austad, a healthy-aging-focused biologist at the University of Alabama at Birmingham, and scientific director of the American Federation for Aging Research.

We may not even have to wait decades for anti-aging drugs to extend our healthy years. Researchers are finding ways to gather and enlist vast streams of personal health data to help keep people sharp and active well beyond their 70s. "The idea that you can be in your 90s and be mentally agile and physically robust is perfectly realistic," says Leroy Hood, a biologist who at the California Institute of Technology and University of Washington helped pioneer the genomics revolution, and is now CEO of the health-related nonprofit Phenome Health, as well as co-founder of the Institute for Systems Biology. (He's 86.)

Critically, the effort to keep aging at bay focuses not on merely adding years to people's lives, but also on making those extra years healthy ones. For more than a century, progress in medical science has helped increase average lifespans around the world. But the average number of years of good health people enjoy—their healthspan—hasn't been growing as quickly as lifespan. In the U.S., the average person can expect to experience nearly 13 years of relatively poor health in late life, compared to fewer than 11 years in 1990, according to the Institute for Health Metrics and Evaluation. In poorer parts of the world, the gap between lifespan and healthspan is even larger.

To shrink that gap, aging science is increasingly focused on healthspan rather than lifespan. Healthspan is now an important metric at the World Health Organization, and the subject of published research and scientific conferences. "We don't want to extend the period of decrepitude, that's just making people sick for longer," says João Pedro de Magalhães, a professor of molecular biogerontology at the University of Birmingham in the United Kingdom pursuing potential anti-aging drugs. "Our goal is to extend lifespan while having the health of someone 20 years younger."

Keeping people healthy and independent longer into old age would not only improve the quality of their lives, it would also help to relieve the massive and fast-growing healthcare and economic burdens of poor elder health. The U.S. Centers for Medicare and Medicaid Services (CMS) calculated that in 2020 adults 65 and older accounted for 37 percent of personal healthcare costs, though they were only 17 percent of the population, and annual spending on adults over 85 that year averaged more than $35,000 per person. Those numbers are likely to climb: The number of people who are older than 80 is on track to triple by 2050. Aging also indirectly takes a toll on the millions of people who must become caregivers to elder family members with disabling disease and mobility challenges. About one out of six U.S. adults provides unpaid care to a senior.

Increasing healthspan could also improve health equity. Those with curtailed access to good medical care, nutritious food, clean air, and other resources important to health already bear more than their share of the disease burdens of age. According to figures from the U.S. Centers for Disease Control and Prevention (CDC), Black Americans are 80 percent more likely to be diagnosed with diabetes than White Americans, with most cases involving older adults; similar disparities exist with other common diseases of older age. Extending health into later years can help ameliorate some of those disparities. "Good health underlies everything important to what it means to be human, from early development to education to jobs to being part of a community," says Hood. "Good health should be part of old age, too."

Science is exploring two different paths to growing healthspan. One is to attack the aging process directly, by identifying the biological mechanisms that drive it and finding drugs that slow them down—which should also fend off the diseases that tend to come with aging, as most significant diseases do. The other is to shift healthcare away from simply treating a patient's disease after symptoms have emerged in older age, toward a "scientific wellness" approach involving heading those diseases off earlier on through the use of data-driven diagnostic tools, precision medicine and tailored lifestyle coaching. Will these efforts be enough to close the healthspan gap?

Slowing the decline

Aging isn't a disease, but it's the major pathway to disease. "The biology of aging is at the core of most diseases that lead to a decline in a person's ability to function well, "says Matt Kaeberlein, a former professor of biogerontology at the University of Washington, who left in 2023 to become CEO of Optispan, a company dedicated to developing ways to extend healthspan. Aging is the biggest risk factor for nine of the ten most common causes of death. "Aging probably isn't just a risk factor for most of those diseases, but a cause. The more precisely we can understand the biological mechanisms of aging, the more precisely we can target interventions."

Although scientists are beginning to unravel those mechanisms, many remain a mystery, says the University of Birmingham's de Magalhães. But science, he adds, has moved much closer to penetrating that mystery by making a big conceptual leap: seeing aging not as an inevitable wearing out of the body's components, akin to the way a car deteriorates with decades of use, but rather as a specific set of biological processes that evolution has programmed into our genes.

> "We don't want to extend the period of decrepitude, that's just making people sick for longer. Our goal is to extend lifespan while having the health of someone 20 years younger."

If that's true, then it should be possible to find drugs that interfere with that programming—a focus of de Magalhães's lab and several others around the world. "We're using computational and experimental methods to identify new compounds that work as longevity drugs," he says.

Evidence is building that such drugs would also act to preserve health, and the drug that many anti-aging researchers consider the most promising is ra-

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pamycin. It was approved in 1999 for suppressing the immune system of patients receiving kidney transplants to avoid rejection of the transplanted organ. It is also used for treating and preventing certain cancers. In 2003 a study found that roundworms exposed to rapamycin lived an astonishing ten times longer than their average lifespan of less than two weeks. The reason it works is not understood, but it has since been shown to stretch the healthspan—as measured in extended periods of normal activity and the absence of significant disease—of several other animals, including flies and mice. It's currently under study in dogs and monkeys. "If it works in those studies, I think we'd have a case for trying it on people," says de Magalhães.

The University of Alabama's Austad agrees that rapamycin is ripe for a human trial as a longevity drug. The FDA has yet to approve such a study, even though the drug is already approved for other purposes, because rapamycin has been associated with an increased risk of cancer and infection, among other side effects. But those problems were observed at high doses in people who already had serious health conditions, Austad notes. "Rapamycin has a bad reputation among a lot of clinicians. But at lower doses it might prolong life without those effects," he says.

The FDA recently approved a University of Washington study of rapamycin's ability to slow periodontal disease—and the study is likely to gather data that could shed light on the drug's anti-aging effectiveness. Still, the agency is likely to set a high safety bar for trials of longevity drugs involving healthy people, to avoid a risk of the trial doing more harm than good to participants.

Meanwhile, because rapamycin is approved for some uses, doctors can legally prescribe it for "off-label" use—that is, for any health purpose they consider potentially beneficial and reasonably safe. There are no official figures, but social media accounts and anecdotal information suggest that at least hundreds of people are getting the drug in hopes of reaping healthspan benefits. Any anecdotal results aren't likely to be taken as scientific evidence, and most anti-aging researchers don't advise taking the drug off-label. "I don't take it myself, and I wouldn't recommend it," says de Magalhães.

Is rejuvenation possible?

Researchers are also paying attention to drugs that kill senescent cells—cells that have stopped dividing. Senescent cells proliferate with aging, and the hope is that by removing them, so-called senolytic drugs can provide healthspan benefits. So far there is little clear evidence that these drugs slow aging in humans, but they do seem to have some beneficial effects in a variety of diseases in animals, including cancer and heart disease. Because some senolytic drugs are found naturally in foods or have been approved to treat specific diseases, and generally have few serious side effects, the FDA has approved dozens of ongoing trials of senolytic drugs against a range of diseases of aging.

Another drug approved for a human longevity trial is metformin, a first-line treatment for type II diabetes taken by about 150 million people worldwide, generally with good results and few significant side effects. The drug has shown some evidence of extending lifespan in animals, and a six-year nationwide trial of its anti-aging properties overseen by Wake Forest University is in the planning stage.

Other potential approaches to slowing aging are under study. One is the "reprogramming" or "rejuvenation" of aging cells through chemicals shown to

[INFOGRAPHIC]

The Conditions That Shorten Our Healthspans

To understand why healthspan has not kept up with increases in lifespan, longevity researchers need to know what issues are making people become chronically ill or disabled. The Institute for Health Metrics and Evaluation, a research organization at the University of Washington, has compiled data on people living with diseases and conditions that affect their health—a metric researchers call "years lived with disability." As a population ages, these conditions pose a heavier burden. **By Katie Peek**

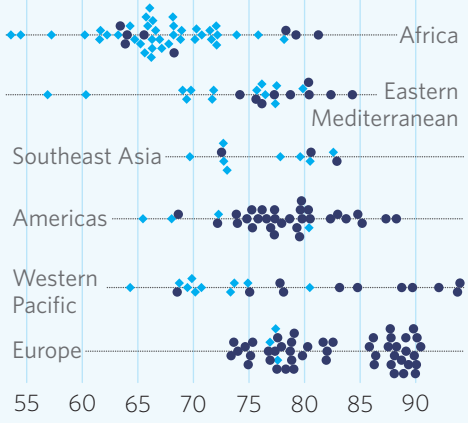
- Communicable, neonatal, maternal and nutritional diseases

Noncommunicable diseases

- Neurological disorders
- Musculoskeletal disorders
- Sense organ diseases
- Cardiovascular diseases
- Diabetes and kidney diseases
- Substance use disorders
- Mental disorders
- Chronic respiratory diseases
- Other noncommunicable diseases
- Injuries (vehicular, self-harm and unintentional)

Healthy life expectancy at birth

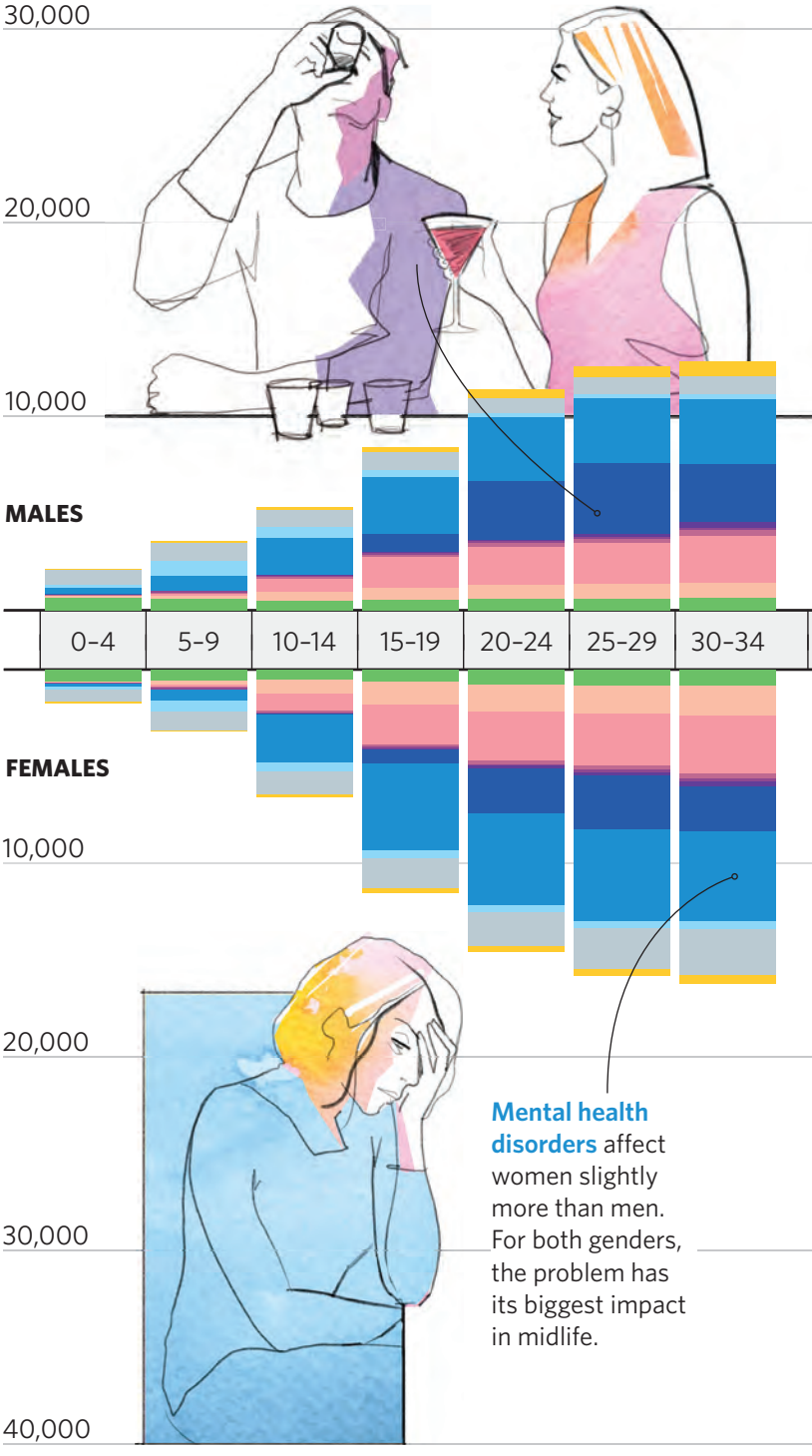
Healthspan is also a matter of geography. Residents of wealthier countries (*circles*) tend to have longer heathspans than those in poorer countries (*diamonds*).



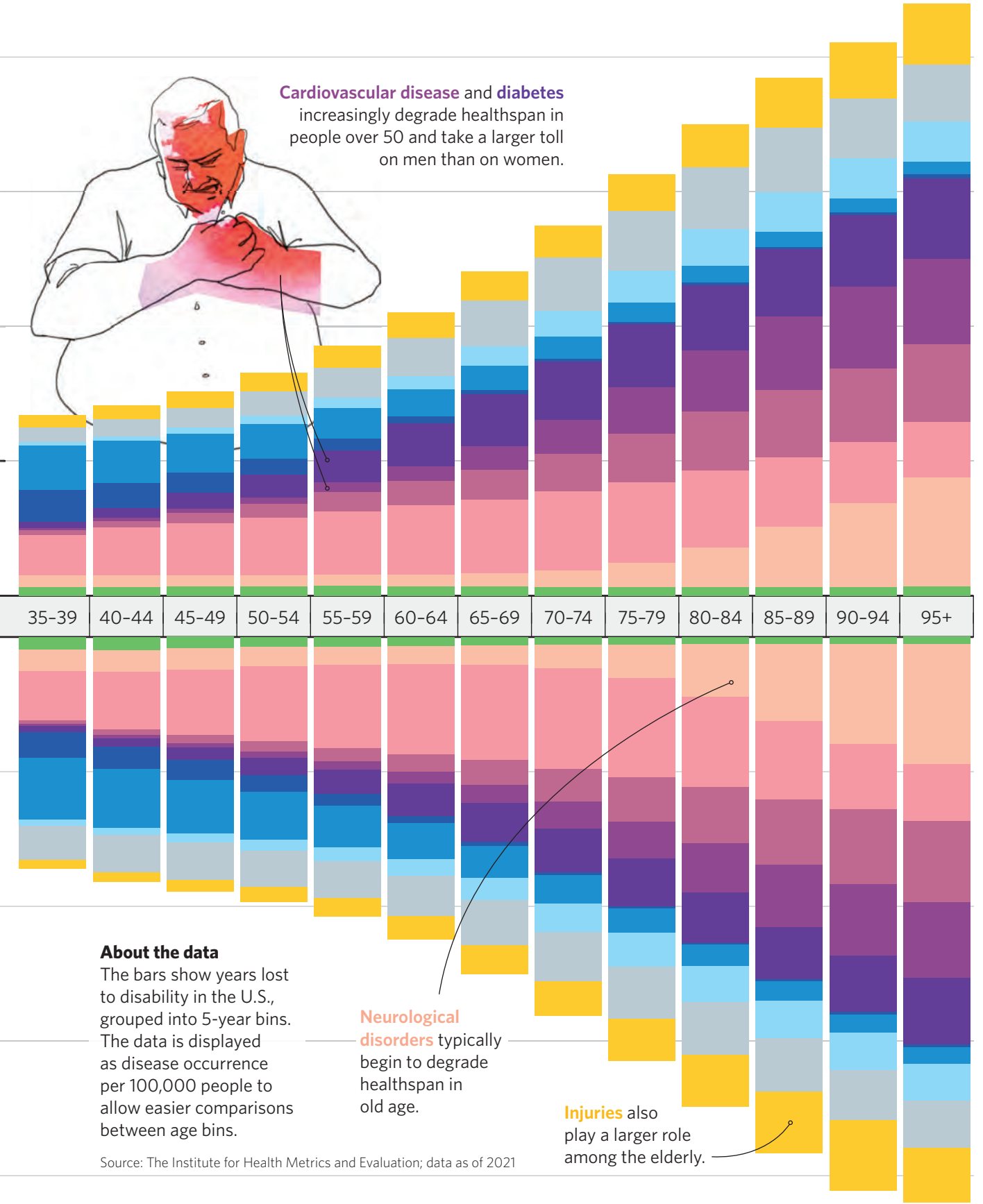
Source: The World Health Organization; data as of 2021

Years lived with disability per 100,000 people, by age group

For both men and women, **substance use disorders** have the biggest impact in their late 20s and early 30s.



Mental health disorders affect women slightly more than men. For both genders, the problem has its biggest impact in midlife.



Source: The Institute for Health Metrics and Evaluation; data as of 2021

cause cells to revert to youthful states. While the technology works well in test tubes, results have been mixed in animals, showing some benefits, but also leading to tumors and other problems. The Silicon Valley biotech company, Altos Labs, whose major investors reportedly include Jeff Bezos, proclaims its intention "to transform medicine through cellular rejuvenation programming." But no clinical trials of the technology have been approved.

And then there is transfusing blood plasma from the young into the old. For reasons that aren't fully understood, that technique has shown a range of health improvements in mice, including longevity, and a small number of clinical trials have suggested people might gain health benefits, too. Because transfusions are a well-established and generally safe procedure, clinicians can perform them today on people hoping to gain benefit, and they've been offered by private companies and clinics. Austad says the evidence from mice is impressive. He expects to see clinical trials aimed at demonstrating healthspan extension. But the need to collect substantial amounts of blood plasma from healthy young people, who are typically paid well to provide it, can propel the cost of treatment into the tens of thousands of dollars. It also raises questions about the ethics of a market for youthful plasma aimed at the wealthy.

Holding illness at bay

Compared with the anti-aging approach, scientific wellness is less ethically fraught. Healthcare in the U.S. and most of the world is reactive: It is designed to spring into action when someone has a detectable health problem. Under that paradigm, the ills of older age are seen as nearly inevitable, and when they emerge, the healthcare system does what it can to treat them.

But those ills might be a great deal less inevitable, or at least delayable for a decade or more, if the healthcare system instead focused on trying to head them off at the pass—that is, when we are still relatively healthy. "Moving from a 'sick-care' system to one that focuses on wellness and prevention plays right into healthspan," Hood says.

The key, says Hood, is making use of massive amounts of personal health data that go far beyond what is normally gathered from most patients. His organization, Phenome Health, is researching techniques for acquiring and analyzing many pieces of information about a patient that can possibly shed light on their health, including genes, proteins, other chemicals, bacteria, brain functioning, heart rhythm, sleep, food, stress, movement and much more. It's a full picture of a person's current state of health known as their phenome. "That data reflects where you stand in your health trajectory, where it's heading, and what can be done to optimize it," says Hood.

The results could help people keep serious illness at bay into their 90s, he says: "It would allow going way beyond anything traditional healthcare can do. It can find out everything that's limiting many aspects of health, and correct it." Interventions might range from drugs to surgery to lifestyle adjustments—often not to treat a problem, but to prevent it from ever emerging in the first place.

> "The biology of aging is at the core of most diseases that lead to a decline in a person's ability to function well."

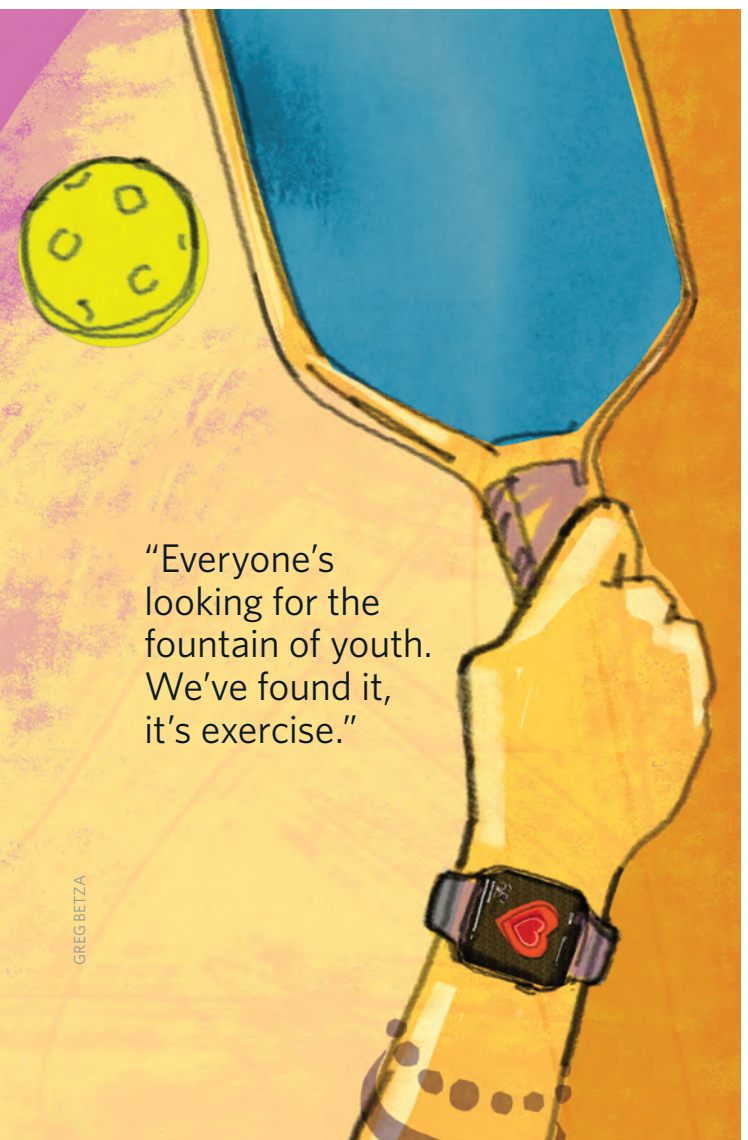
Optispan CEO Kaeberlein says his company is already putting a similar approach into action with patients who sign up for its services. In addition to extensive patient testing and ongoing monitoring, the company is also looking to integrate anti-aging treatments as they become available. As a biogerontologist, Kaeberlein has spent years researching potential healthspan drugs, including studying rapamycin's effects in dogs and trying the drug himself to successfully treat a shoulder injury. "There are different ways to modify the pathway of aging to increase resilience and even recover organ function," he says. "But the biggest benefits come from doing it proactively, through advanced screening and early interventions."

Gathering patient data in these proactive approaches often begins with a genomic analysis to look for genetic variations that provide insights into a person's unique health risks. "Your genome can tell you what your potential health trajectories are," says Hood. "But it's your behavior, your environment and your healthcare that will impact which of those trajectories you follow in later life."

Blood tests are of course part of the process, too. But these tests can and should go well beyond the traditional workup, says Hood. "We now know how to interrogate your entire biological system through blood. Hundreds of different molecules are constantly

being secreted into your blood by your organs, and that provides us with a window into health and developing disease." In addition to highlighting the levels of the many proteins that control virtually every bodily function, a blood test can also pick up environmental toxins, as well as any of thousands of metabolites—the molecules that circulate in the body when it breaks down tissue or anything that has been ingested.

A census of the range of bacteria living in a patient's gut—that is, the microbiome—can be another essential tool in a preventive approach to delaying the ill effects of aging, usually obtained through a stool sample. In recent years research has made clear that variations and changes in the microbiome can be linked not just to gastrointestinal health, but to diabetes, heart disease and Alzheimer's, among other disorders. Some of these problematic microbiome variations can be addressed through diet or drugs. "The microbiome is the barrier between what you take in and what makes it into your system," says Hood. "It profoundly impacts well-being, and analyzing it is critical."



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Lifestyle, too, plays an outsized role in preventive health. Diet, exercise, sleep, stress and social support are all key factors. Both Phenome Health and Optispan are developing ways to analyze and fine-tune each of them for individual patients. Adding or adjusting exercise may be an especially effective way to stretch healthspan, according to Keith Diaz, an associate professor at Columbia University Medical Center, and director of the Cardiology Division's Exercise Testing Laboratory. "Everyone's looking for the fountain of youth," says Diaz. "We've found it, it's exercise."

Diaz has run studies that show exercise can set back biological age by up to 30 years. "The benefits go through every system," he says. "Just replacing 30 minutes of sitting with light-intensity exercise lowers the risk of death by 35 percent." Reaping the benefits of exercise doesn't require banking an entire lifetime's worth of workouts. According to Diaz's research, people who are older when they start exercising still get a payoff in improved health, including longevity and healthspan.

A lab on your wrist

The data-driven, preventive-care approach to healthspan is getting a big boost from the availability of sophisticated wearable devices capable of continuously measuring a wide array of biological and behavioral details. That includes heart-rate variability, respiration rate, blood oxygen saturation, body temperature, stress levels, sleep stages, energy expenditure, and much more. Devices that continuously monitor blood-sugar levels are particularly helpful. "People can see in real time what's happening in their blood an hour after eating garlic bread or ice cream," he says. "It helps them adopt much healthier diets."

The data from wearables can typically be uploaded to a patient's clinical care team, so that it can be added to lab data and medical history to provide a clearer picture of what might need tweaking for maximum healthspan benefits. "We know how to interpret this data to optimize personal health," says Kaeberlein.

Diaz sees wearables as a game-changer for exercise. "Personalizing every person's exercise program is the next frontier of exercising for health," he says. "The amount and type of exercise that's ideal is different for each person, and we'll be able to find what's best for each one." He adds that analyzing a person's movements throughout the day can also lead to an exercise program that they are more likely

to stick with. The data can reveal patterns in where and when someone seems to have more energy, for example, and what sort of activities get them moving more and provide bigger health benefits.

Hood also emphasizes cognitive and emotional assessments to monitor and protect brain health. "Assessing brain health and general mental state is absolutely lacking in contemporary medicine," he says. Phenome Health provides a series of 40 brain assessments, from memory to reaction time to visual keenness, to spot potential problems and head them off with a tailored program of brain-stimulating exercises. "People tend to start fading cognitively in their mid-30s because they don't exercise their brains in the right way," he says.

Other screening tests rarely given as part of a standard physical can be critical to getting ahead of any impending diseases of older age, says Kaeberlein. He advocates routine ultrasound imaging to detect, for example, a fatty liver—a problem that he says impacts more than a third of adults in the U.S. He also pushes for regular body-composition scans via low-dose X-ray, a relatively inexpensive test that can reveal excess fat deposits and bone-density issues, both of which can lead to serious problems in older age but can be effectively addressed before then.

Kaeberlein expects to soon be able to add "liquid biopsies" to that list of screening tests—a developing technology that enables detecting signs of even a tiny cancer lurking somewhere in the body from a blood sample. "There are 20-some cancers these tests can detect with reasonable accuracy and precision, and if caught early they can usually be cured," he says.

AI is already bolstering efforts to optimize preventive care in pursuit of longer healthspan. Optispan is developing AI tools to discover new links between factors that can be measured in patients and the disease risks they face. It is also creating AI tools that can help conventional healthcare providers offer data-driven prevention without having to undergo extensive retraining—with the goal of eventually enabling people do it themselves. "We want to create personalized 'healthspan agents' for individuals that can gather and analyze any health data they're willing to share," Kaeberlein says.

Finding ways to automate preventive health tools that can extend healthspan could go a long way to improving health equity. AI tools could slash the costs of providing personalized, data-informed care to patients, which would benefit those without great resources, top-notch healthcare insurance and ready access to clinicians. AI can also learn to adapt recommendations to a patient who may not have the best healthcare resources at their disposal. "We want to optimize advice for healthspan, but we also want to tailor it to economic status, among other things," says Kaeberlein.

Planning for significance

The biggest challenge in bringing healthcare-extending treatments and care to a large percentage of the population may simply be getting the healthcare system—and even patients—to embrace these new approaches. "We need a healthcare system that's predictive, preventive, personalized and participatory," says Hood. "We know how to do the first three, but getting physicians, hospital leaders, patients, regulators and insurance companies to participate is a nightmare." Hood predicts the healthcare system will move in the right direction, but it will take ten or more years to begin the transition.

> "Your genome can tell you what your potential health trajectories are. But it's your behavior, your environment and your healthcare that will impact which of those trajectories you follow in later life."

When the healthcare system does finally succeed at giving people an extra decade or even two of good health, a new challenge may emerge, says Hood. "When we get those extra years, what will we do with them?" he asks. "A key part of being healthy in your 90s is having a purpose in life, which means being involved in something that's interesting and productive." That could mean continuing to work, or finding hobbies or sports to be passionate about, or seeking more education, or building new relationships and community connections.

In other words, when we maintain the health of younger people into older age, we will also have to be ready to maintain their pursuits. "People in their 90s will have to continue to find significance, however they want to define it for themselves," says Hood.

That may be a challenge. But it's a challenge most of us would like to have a chance to face.

David H. Freedman is a freelance writer.

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Lifelong Lobstering

On June 6, 1920, Virginia Oliver was born in Rockland, Maine. When she was eight, Oliver joined the family business with her lobster-catching father and brother. It became a lifelong passion.

"I like being along the water," she said in an interview in her home with author Barbara Walsh. "It's beautiful. Some people never, ever get to see the sun rise out there. There's nothing like it."

She also wanted to be in charge. She eventually became the captain of her boat, which her late husband had named Virginia. "I'm the boss," she said. "I'm kind of independent, you know."

Though a fall kept Oliver off her lobster boat for the 2023 and 2024 seasons, she hoped to return to the ocean in the summer of 2025 at the age of 105.

"You can't sit around watching TV all day," she said. "You've got to keep moving, otherwise you'll end up in a wheelchair."

Sources: Barbara Walsh and her book *The Lobster Lady: Maine's 102-Year-Old Legend* (Irish Rover Press, 2022)

A Return to Holistic Medicine

The power of artificial intelligence to analyze data on genomes and phenomes is driving a shift to prevention and personalized care

BY JAMES YURKOVICH AND LEROY HOOD | ILLUSTRATIONS BY JOEY GUIDONE

Ancient medicine as practiced by the Chinese and Greeks thousands of years ago emphasized the importance of restoring balance and harmony in the body through a delicate blend of healing and careful observation. Greek physicians, influenced heavily by Hippocrates, incorporated diet, exercise, environment and lifestyle into health plans and emphasized the connection between physical and mental well-being. In subsequent centuries, the focus of health care shifted to acute and chronic diseases, which remains the norm today.

In the last few decades, however, the emerging field of "scientific wellness" has begun to bring us back to the ancient notions of balance and harmony. Studies suggest that health is a combination of genetics (equivalent to what the ancients called fate), behaviors, and environmental exposures for each individual. As a result, many of the central tenets of ancient holistic approaches to medicine are once again entering mainstream thinking of scientists and physicians. We are starting to appreciate that the human body is a unified system that we can assess through observation and come to understand through holistic systems-biology approaches.

Driving this newfound appreciation for holistic medicine is the power of individual data-driven medicine. By sequencing each patient's genome, a doctor can obtain advance warning of disease risks and information on the relative efficacy of different treatments. By routinely gathering tens of thousands of signals on a patient's physiology, behaviors and environmental exposures, the doctor can come to a deep understanding of a patient's phenome—the collection of all the dynamic characteristics of an individual's biology.

By sequencing each patient's genomes, a doctor can obtain advance warning of disease risks and information on the relative efficacy of different treatments.

With a detailed picture of a patient's genome and phenome, a physician can optimize wellness and healthy aging for each person by ameliorating the deficiencies that data-driven health reveals. In many cases, the doctor can anticipate disease before it advances far and nip it in the bud. When a patient is on the cusp of a transition that may lead to disease down the road, the doctor can intervene with preventive measures—including lifestyle changes, dietary modifications and preventive treatments—to reduce the likelihood of the onset of disease. Personalized recommendations based on the unique features of each patient's genome, behaviors and environmental exposures give a picture not only of current disease but also the health trajectory of a patient that may lead to wellness optimization, healthy aging and ultimately lead to prevention of disease. Such an approach has the added benefit of enlisting the active participation of patients in their own healthcare decisions.

Most doctors don't yet practice this way, of course, but as our technology and knowledge advance, more and more will. This kind of high-tech, holistic approach is already beginning to transform healthcare from a reactive model focused primarily on treating diseases to a proactive model that emphasizes prevention and personalized care. It is our best bet to help people stay healthy throughout their full lifespan.

A proof of concept

The data-driven, scientific wellness approach to healthy aging has been tested in real-world longitudinal studies in thousands of individuals. A few years ago, the scientific wellness company Arivale, founded by Leroy Hood, Nathan Price and Clayton Lewis, gathered participants and administered extensive testing that measured a wide range of biological and behavioral factors. We were able to show striking improvements in wellness and healthy aging for most of the participants. Over four years of the program, more than 150 people transitioned from wellness to many different chronic diseases. The rich dataset gathered from this cohort allowed us to investigate the complex interplay of genetics, environment and lifestyle in determining health outcomes.

The statistical analyses of the data yielded correlations that could be translated into hundreds of actionable possibilities—behavioral or clinical intervention strategies for reaching specific improved wellness and aging outcomes. For instance, ten people we had been routinely testing developed some form of cancer. We went back over the data we'd collected prior to their diagnoses and found multiple elevated physiological signals that had occurred months or years before their cancers were clinically apparent. As a result, doctors can now test for these signals, or biomarkers, in their patients to detect early signs of cancer before the onset of disease, giving them an opportunity to develop preventative interventions. Given that the treatment of chronic diseases consumes well over 80 percent of the $4.5 trillion spent each year on healthcare in the U.S., this approach could lead to substantial savings.

One of Arivale's major accomplishments was to develop a model that could predict an individual's biological age—the age your body says you are, as distinct from your calendar age. The lower a person's biological age is relative to chronological age, the better they are aging. It was found that biological age was correlated with wellness and disease phenotypes, suggesting that it may be a more accurate indicator of health status than chronological age. This approach allows for the calculation of not just overall biological age but also ages specific to each organ. In other words, your heart might be "younger" than your birthday, but your liver may be several years "older". With this data come various possibilities for taking action that can lower one's biological age globally or in individual organs. For instance, during Arivale's wellness program, women lost an average of 1.5 years of biological age per year.

Another key finding was the derivation of an algorithm for accurately measuring an individual's body fat. The classical body-mass index (BMI) calculation,

The microbiome's ability to enhance or diminish the effect of statins on LDL cholesterol may be more pronounced than any genetic predisposition.

which uses height and weight measurements, does not accurately assess about 30 percent of the population, mainly because it doesn't distinguish weight from muscle or fat. Our alternative, biological BMI (bBMI), is more responsive to metabolic changes and can accurately assess all individuals. This is a powerful metric to use in the context of the new anti-fat drugs.

This research further led to discoveries of relationships between the gut microbiome and the response to common pharmaceuticals such as statins. The microbiome's ability to enhance or diminish the effect of statins on low-density lipoprotein (LDL) cholesterol may be more pronounced than any genetic predisposition. Studies demonstrated associations between the composition of gut microbiota and factors such as body mass index, sleep duration, healthy aging and risks of developing certain diseases.

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Other studies contributed to our understanding of the genetic basis of health and disease. Large populations studies (including hundreds of thousands of people) have identified collections of genes (10s to 100s) that contribute to many chronic diseases and from these polygenic scores one can derive the genetic risks of individuals for these diseases with their whole genome sequences. We found these genetic risks can influence how people respond to lifestyle interventions. For example, those with genes that confer a high risk for high LDL cholesterol (a proxy for heart disease) and high levels of LDL cholesterol in their blood can only bring it down by using drugs such as statins; in contrast, for those with low-risk LDL genes, diet and exercise can suffice. This raises the possibility that treatments should vary from one person to the next depending on their genetic profiles. We are now beginning to obtain data that will prove valuable for identifying the early stages of chronic diseases (such as diabetes, cancer, Alzheimer's disease and heart disease), which may open the door to identifying biomarkers that could be used for early detection and intervention.

Researchers at the Institute for Systems Biology are now exploring ways of assessing a person's frailty, which we define as the diminishment of certain vital functions. Based on measurements of various molecules in the blood, a measurement of frailty would be independent of chronological age. We are also developing an AI algorithm that can quantify fragility, which we think would yield a deeper understanding of the underlying biological processes associated with aging.

The right kind of data

Artificial intelligence technologies rely on data to train predictive models. But human biomedical datasets tend not to represent the full diversity of the human population. Even though people who are white or of European descent make up about a quarter of the world population, they account for three-quarters of the world's sequenced genomes. With such an imbalance, we cannot hope to develop therapeutics that are effective for everyone.

Developing diverse datasets is also central to building accurate models of human diseases. Studies have shown that people with the *APOE* gene, which provides instructions for making a protein that helps transport cholesterol and fats in the bloodstream and is a risk factor in Alzheimer's disease, generates very different genetic risks across different ethnicities. Individuals of Japanese descent who have the two bad copies of the *APOE* gene are almost three

times more likely to develop Alzheimer's than white people with the same genes. By contrast, among Hispanic populations with the same genetic profile, there appears to be no risk. South Asian populations show a higher prevalence of diabetes.

Sex is another fundamental biological variable that can significantly influence gene expression and phenotypic outcomes. Ignoring sex-based differences in data can lead to biased models that fail to generalize to diverse populations. In 2016, the National Institutes of Health in the U.S. mandated that researchers include sex as a biological variable and justify single-sex investigations. Before that, however, biomedical studies were conducted almost exclusively on male animals and humans. As a result, almost all aspects of women's health—from reproductive health and pregnancy to menopause—are data deserts for scientists.

Socioeconomic status is another complex factor that can influence health and disease. Its impact on access to healthcare, nutrition, and environmental factors are well documented. Healthcare data scientists are just beginning to accumulate the genome and longitudinal phenome data that will provide a myriad of new insights in this area.

Overcoming bias in AI models presents a related challenge. Because models trained on biased data can perpetuate existing inequalities, we can help to mitigate bias by ensuring that the data used to train AI models is representative of the broader population. We must also establish standards of data collection so datasets gathered by different groups of scientists representing diverse racial populations can be compared and analyzed with one another.

Data-driven medicine is likely to help drive down costs of healthcare and increase efficiency, but we do not yet have the financial data to make a strong economic argument. According to a 2021 report from Deloitte, a shift to wellness-focused healthcare in the U.S. could save trillions of dollars in chronic-disease care, potentially shifting that spending to wellness, healthy aging and disease prevention. The way to generate data to back up this claim is to target major chronic diseases that are associated with unhealthy aging, such as diabetes and Alzheimer's.

Phenome Health is advocating a large-scale research and clinical project, Human Phenome Initiative (HPI), to improve the quality and magnitude of health-related data. The HPI would generate a comprehensive database of genomes and phenomes that can be linked to clinical, mental, sociological, and environmental information. The goal is to collect and analyze phenotypic data on a diverse population of a million or more individuals over a span of 10 years. The hope is that this biomedical resource will provide compelling data for strikingly improving individual wellness, healthy aging and initiate widespread early detection and prevention of chronic diseases. HPI may also provide the data necessary for researchers to identify the causal factors that contribute to various diseases and health conditions through the deployment of new AI techniques.

HPI hopes to generate the right kind of data to power the next wave of health and biotechnology breakthroughs. The data and resulting insights will lead, we believe, to the validation of scientific wellness to improve the healthy aging of each individual. It will demonstrate the tremendous healthcare cost savings that come from preventing chronic diseases.

Developing diverse datasets is central to building accurate models of human diseases.

It will catalyze the cost reduction of phenomic-profiling technologies, making the technologies more accessible. And it will move wellness and prevention into the home by empowering individuals with new digital health technologies. Just as the Human Genome Project initiated a 100-million-fold decrease in the cost of DNA sequencing, we believe HPI will also lead to a exponential decreases in phenomic technologies.

AI-driven healthcare

Wearables and AI avatars have a tremendous potential to democratize healthcare. By collecting and analyzing vast amounts of data, wearables and AI avatars can make it possible to detect health problems

We are moving toward a transformation from the current disease-oriented healthcare system to one that actively optimizes for wellness and healthy aging and prevents disease.

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early, develop treatment plans tailored to each individual, and provide remote (at-home) monitoring. They can also potentially lower healthcare costs, increase access to care, and advance medical research. Addressing challenges such as data privacy, interoperability, and ethical considerations is crucial to fully realizing the potential of these technologies.

Ensuring the security of personal health data requires robust measures and explicit informed consent. Seamless data sharing and communication across different devices and platforms, which is crucial to achieve the full potential of these technologies, requires standardized protocols and data formats. It's also essential to address biases in AI algorithms, prevent discrimination and protect patient autonomy.

In the future, each of us might have an AI avatar that acts as a health companion, collecting and analyzing data from our wearable devices, electronic health records, and other sources of data. Using advanced algorithms, such a health companion would make recommendations about sleep, managing stress, diet, exercise and repairing deficiencies arising from one's genome or phenome. It would track changes in an individual's health over time, identifying potential risks and areas for improvement as they occur.

The AI companion would also serve as a bridge between people and their doctors. For example, if it detected a decline in heart rate variability, it might recommend stress-reduction techniques and schedule a check-up with your cardiologist. By providing personalized guidance and support, it could help individuals take a more proactive approach to their health and well-being.

The healthy-aging approaches of gerontology (study of aging) and scientific wellness will soon converge. As a result, the human healthspan will be extended into the 90s and beyond. People will live productive and creative lives for 20 or more extra years than they do now.

We are moving toward a transformation from the current disease-oriented healthcare system to one that actively optimizes for wellness and healthy aging and prevents disease. Through continued advancements in technology, this data-driven health approach will be democratized and made accessible to all populations. In five years, millions of patients across the world will probably have access to the kind of clinical care we have been describing in this article. Scientists will also be able to execute nationwide data-driven health studies.

Finally, the widespread deployment of AI will catalyze change in almost every aspect of healthcare, including using AI to empower any physician with the domain expertise necessary to take a holistic approach to practicing medicine—just as our predecessors did thousands of years ago.

As more and more people live longer, healthier lives, we may eventually need to grapple with a different problem: What to do with that extra decade or two of healthy life?

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Leroy Hood is the founder and chief executive officer of Phenome Health, distinguished professor at the Buck Institute and co-founder and professor at the Institute for Systems Biology.

A New Science of Youth

Findings from the emerging field of geroscience suggest that some aspects of aging may be reversible

BY ERIC VERDIN AND GORDON LITHGOW | ILLUSTRATIONS BY JOEY GUIDONE

For most people, aging means inevitable and irreversible decline. Our bodies wear down, our cells malfunction, and we become more susceptible to diseases. But new research from the emerging field of geroscience is modifying this narrative. If this new research bears fruit, it would mean progress toward a goal that's as old as humanity: to add years to people's lives, and ensure that those years are filled with vitality and independence.

Geoscience rests on the notion that aging itself, rather than individual diseases, is the root cause of many chronic conditions. To explore this hypothesis, scientists have focused on understanding and targeting the biological mechanisms of aging with the goal of extending both lifespan and healthspan, or the number of healthy years.

Extending healthspan would improve the quality of life for millions of people and reduce the burden of aging-related diseases. Baby boomers, most now well beyond the age of 65, are grappling with conditions like heart disease, type 2 diabetes, cancer, Alzheimer's, and frailty, which not only reduce quality of life but place immense pressure on families, healthcare systems and economies.

Many geroscientists believe that the biological mechanisms of aging are both malleable and treatable. Researchers in clinics and laboratories around the world are now testing this notion. If it turns out to be correct, it could be possible to slow aging or even reverse it.

Targeting aging itself

Since biological aging is the primary mechanism for the emergence of chronic diseases over time, according to the geroscience hypothesis, understanding its associated molecular pathways is essential. By addressing these underlying processes, we believe we may be able to slow aging itself and delay the onset of heart disease, diabetes, Alzheimer's and many other aging-related diseases. Rather than tackling each one of them individually, we should make what's common to them all the main target: the aging process.

Research has shown that aging is driven by a series of interconnected biological processes that begin early in life and build up over time. Scientists have identified a dozen of these processes, often referred to as the hallmarks of aging (see 'What Drives the Aging Process?' on page 27). As our bodies age, damage accumulates to our DNA from radiation, errors during replication, and oxidative stress. Our mechanisms of repairing this damage grow less efficient. Protective caps on the ends of our chromosomes, called telomeres, shorten. The ability of our cells to produce proteins to carry out metabolic functions degrades. Our mitochondria—the powerhouse of our cells—can become dysfunctional. The stem cells necessary for tissue regeneration and repair lose their capacity to self-renew and differentiate. Our gut bacteria can become imbalanced. The ability of our cells to communicate with one another can be disrupted.

> Rather than tackling heart disease, diabetes or Alzheimer's individually, we should make their common thread—the aging process—the main target.

These developments increase our bodies' susceptibility to disease. Many of them promote inflammation, inhibit tissue repair, promote insulin resistance and impair our stress response. These changes can increase our susceptibility to a host of age-related diseases, including neurodegenerative disease like Parkinson's and Alzheimer's, as well as diabetes, cardiovascular disease, macular degeneration, and many forms of cancer.

By deepening our knowledge of these processes of aging, we are identifying targets for treatments that slow them down. One promising target is senescent cells. These are cells that stop dividing but refuse to die. Instead, they remain active, secreting molecules that lead to inflammation and contributing to tissue damage and age-related diseases. Scientists believe that the accumulation of these senescent cells is a major driver of aging and its associated disorders.

The new field of senolytics involves designing drugs that can clear senescent cells out of the body. The late biochemist Judith Campisi and her colleagues at the Buck Institute have successfully used these strategies to extend the lifespan and healthspan of laboratory animals. Unity Biotechnology, a startup, has also successfully targeted an age-related eye disease with senolytics in phase 2 clinical trials (the authors have no relationship to Unity). If all goes well, the work could lead in a few years to treatments to clear out these harmful senescent cells.

Aging is not a one-size-fits-all process; genetic factors and lifestyle choices also play a role in how fast or slowly we age.

Calorie restriction (CR) is one of the most robust interventions for extending lifespan and delaying age-related diseases across a variety of organisms, from yeast to primates. By reducing caloric intake by 20 to 40 percent without malnutrition, CR triggers profound physiological changes, including enhanced autophagy, improved mitochondrial function, and reduced oxidative stress. These effects slow cellular damage and improve metabolic efficiency, contributing to delayed onset of conditions such as cardiovascular disease, diabetes, cancer, and neurodegenerative disorders. Studies in humans, such as the CALERIE trials, suggest CR can improve markers of aging, like reduced inflammation and improved insulin sensitivity, though long-term adherence remains a challenge.

Emerging therapies like metformin and rapamycin seek to replicate CR's benefits without the need for strict dietary intervention. Metformin, a widely used anti-diabetic drug, activates AMPK, a cellular energy sensor, while dampening mTOR signaling—key pathways implicated in aging. By improving glucose metabolism, reducing oxidative stress, and modulating gene expression, metformin shows promise in delaying age-related diseases. The TAME trial is currently testing its potential to reduce the risk of conditions such as cardiovascular disease and cognitive decline in humans.

Rapamycin, a potent inhibitor of mTOR, also mimics CR's effects and extends lifespan in multiple species, even when administered late in life. It enhances autophagy, reduces cellular senescence, and improves immune function. Clinical studies have shown rapamycin can rejuvenate the immune system in older adults and may mitigate age-related cardiac dysfunction. However, its immunosuppressive effects require careful monitoring.

Together, CR, metformin, and rapamycin target the fundamental mechanisms of aging, offering hope for interventions that could extend healthspan and reduce the burden of age-associated diseases.

Tailored interventions

Aging is not a one-size-fits-all process; genetic factors and lifestyle choices also play a role in how fast or slowly we age. Once we have identified specific factors that influence an individual's aging process, it may be possible to tailor interventions that target the unique biological mechanisms at play in each person (see 'A Return to Hollistic Medicine' on page 18). Since the aging process happens slowly, a preventative approach may be able to head off the onset of aging-related diseases and extend the healthy years of life. In addition to aging, other risk factors for disease are specific to the individual, including genetic background and lifestyle. This personalized approach to aging could lead to a new era of medicine, where treatments are designed to extend life and improve its quality by reducing the burden of age-related diseases.

Significant challenges remain. Limited access to treatments could worsen social inequalities. Since age is not a disease per se, current regulations do not currently accommodate treatments for it. For geroscience to truly take hold, regulators will need to adapt to this new way of thinking about health.

Ethical questions about access to treatments must be addressed to avoid worsening social inequalities.

By targeting the fundamental processes that drive aging, we have the potential to transform medicine and society. The future could see longer, healthier, and more vibrant lives, where aging is no longer associated with decline but with continued growth and fulfillment.

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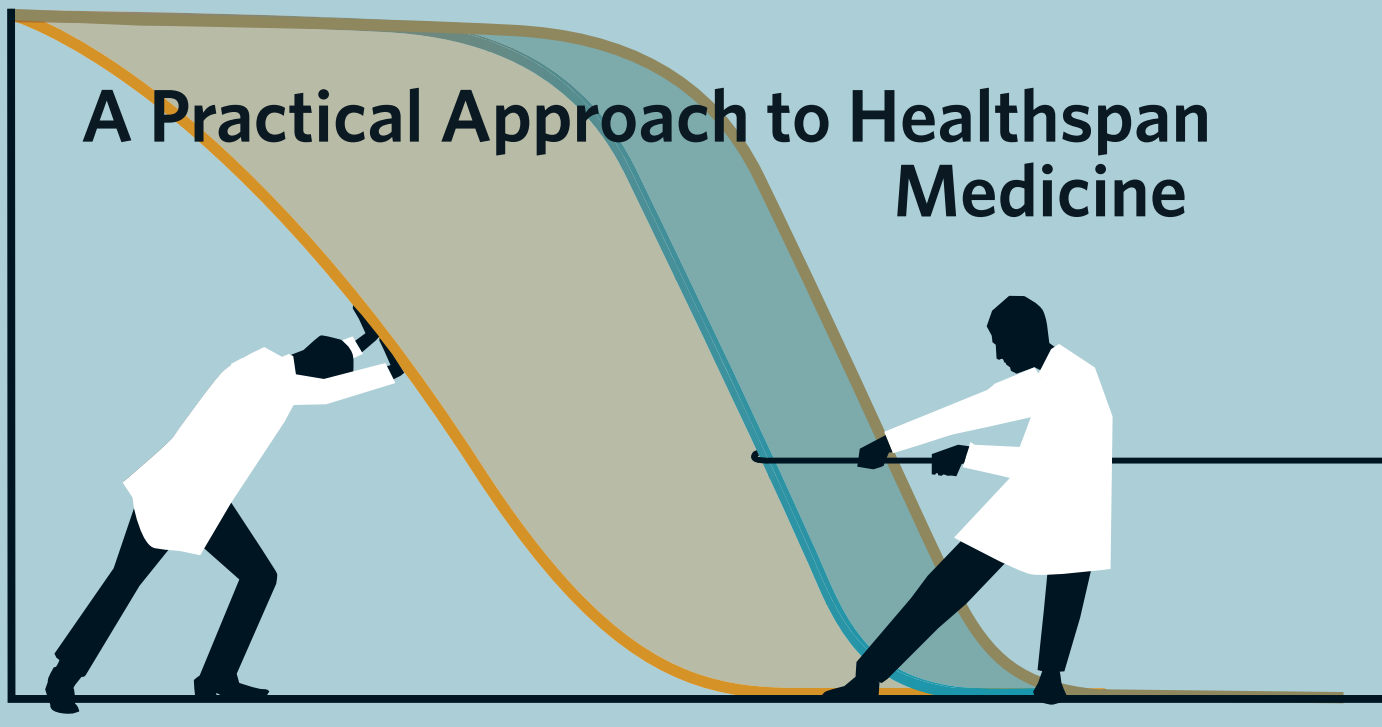
What Drives the Aging Process?

It's one thing to see the effects of aging on the human body, another to identify what causes those effects in the first place. Scientists have identified 12 distinct hallmarks of aging.

Senescent cells	When a cell is no longer capable of division but doesn't die, it can build up in the body and secrete molecules that promote inflammation, tissue dysfunction, and the age-related diseases. The removal of senescent cells has shown promise in reversing some aspects of aging in experimental models.
Telomere erosion	A telomere is a set of DNA molecules that doesn't contain genetic information but functions as a protective endcap to prevent one chromosome from merging with another. Each time a cell replicates, the telomeres in its DNA wear away. Once they lose their protective abilities, the cell can no longer divide: it enters senescence.
DNA damage	Cells also enter senescence as part of what's called the DNA damage response. In a functional cell, mutations and other errors that could cause problems for the organism (such as cancer) occur regularly in DNA. A healthy cell enacts its DNA damage response, halting cell division and keeping the error from spreading.
Epigenetics	The chemical compounds that turn sections of DNA on and off—collectively, the epigenome — change over the course of a lifetime and can hasten or slow the onset of aging. The epigenetic alterations can be passed down from parent to child or can be altered by outside factors such as exercise, environmental exposures, and psychological stress.
Mitochondrial dysfunction	Energy that each cell needs to function comes from its mitochondria—ovoid structures in which biochemical reactions convert nutrients into energy. In older people, mitochondria become less efficient, inhibiting cells from performing their assigned tasks, such as filtering toxins for liver cells.
Protein degradation	Aging cells lose their ability to properly maintain protein quality, resulting in the accumulation of misfolded, damaged, or aggregated proteins. This dysfunction is implicated in diseases such as Alzheimer's and Parkinson's and plays a central role in the decline of cellular and tissue function with age.
Cellular repair	The process by which cells recycle damaged organelles, proteins, and other components becomes impaired, allowing toxic waste to accumulate. The resulting cellular dysfunction and death is linked to neurodegenerative diseases and general cellular aging.
Dysregulated metabolic pathways	Pathways that regulate metabolic processes, growth, and resistance to stress become dysregulated. This can lead to promotion of cellular growth at the expense of repair, impaired regulation of energy and stress response, and other conditions.
Exhausted stem cells	Stem cells, which are essential for tissue regeneration and repair, lose their capacity to self-renew and differentiate, contributing to the degeneration of organs and tissues—particularly the skin, blood, and immune system.
Imbalanced gut microbiome	A decrease in beneficial bacteria and an increase in harmful species in the gut can contribute to systemic inflammation, immune dysfunction, and metabolic disorders. The gut microbiome influences cognitive function, metabolic health and other aspects of wellness.
Poor communications	The endocrine system, which uses hormones to send signals from one part of the body to another, shifts with age. For instance, less melatonin makes sleep cycles more irregular; less growth hormone induces muscles to atrophy.
Inflammation	Low-grade chronic inflammation leads to tissue damage, impaired function and diseases, including cardiovascular disease, diabetes, and neurodegeneration. Many factors contribute to inflammation, including senescent cells, dysfunctional immune responses and altered intercellular communication.



A Practical Approach to Healthspan Medicine

Some physicians are forging a new protocol for keeping their patients healthy

BY MATT KAEBERLEIN

For many people, a car is simply a way to get around. Drive it, fill the tank now and then, and when it breaks down, take it to the shop. When it wears out, trade it in for a new one.

This breezy attitude is fine for cars but a lousy way to run healthcare. Yet that is how medicine has worked in the U.S. for years. When we get sick, we go to the doctor for a fix. The problem is, when our bodies wear out, we can't trade it in for a new one.

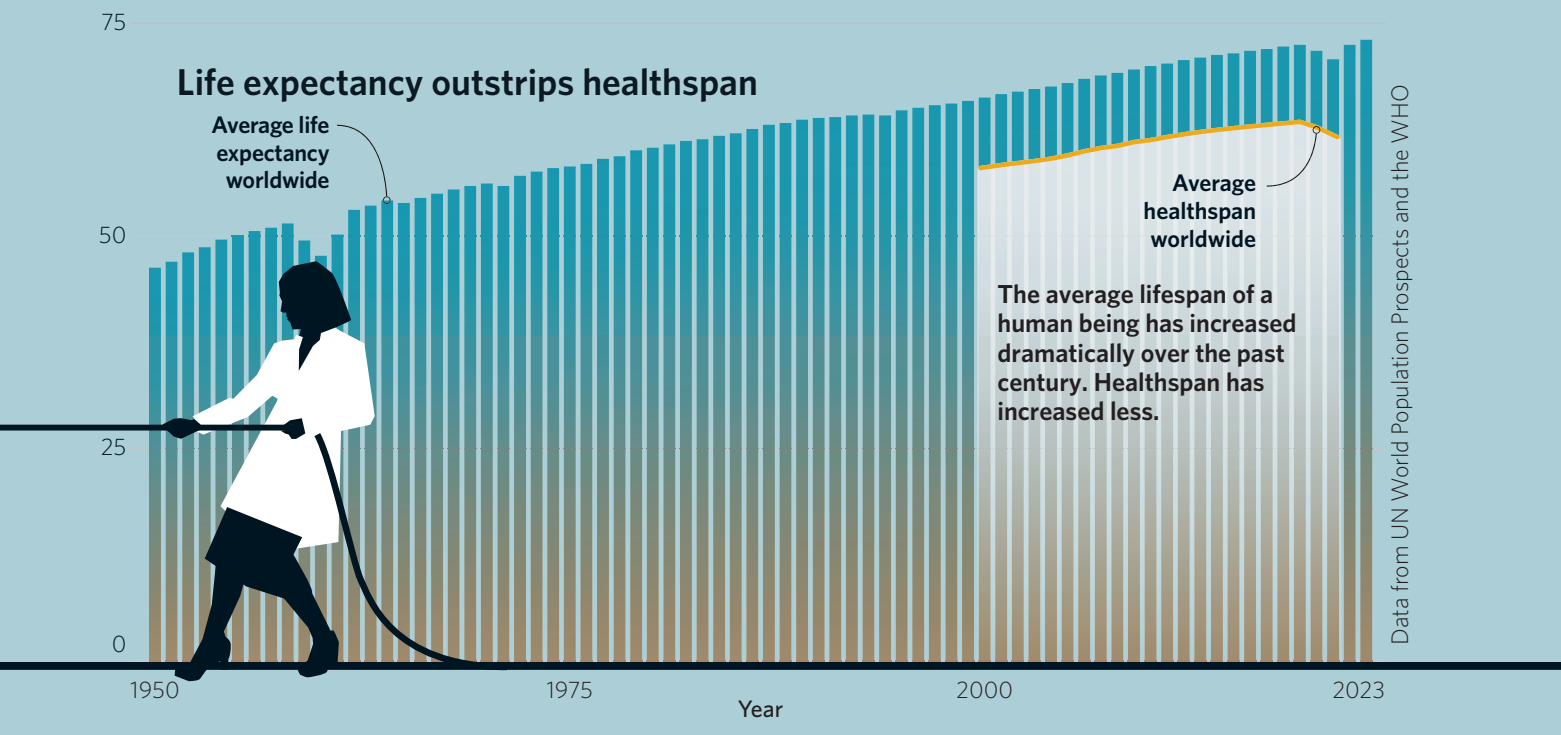
The reactive approach that has characterized U.S. healthcare for decades has worn thin. It is no longer economically sustainable. It has created a situation where more people spend a greater number of years suffering from chronic disease than ever before. As a result, there is a growing movement toward a proactive medicine that focuses on keeping body and mind healthy into old age—increasing healthspan, or years lived in good health, to something closer to lifespan. It's a maintenance program of sorts for the one body you'll ever have.

Healthspan medicine is a work in progress. There is no definitive how-to guide or protocol to follow. We need further discussion among clinicians, researchers, and policy makers, as well as advances in the technologies at our disposal. However, many of the basic tenets are beginning to take shape. These include a focus on early detection through advanced screening and diagnostics, a recognition of the interconnectedness of human biology as a system of systems, and understanding the critical role that aging biology plays as a root factor for most causes of disability and death.

At Optispan, the healthcare technology company I lead, we are developing a best-in-class healthspan medicine program called The Praxis (Latin for "practice"). Our goal is to enable access to rigorous, science-based health optimization for as many people as possible, ultimately scaling it to the point where it becomes a mainstream approach to healthcare. The upside is that millions of people will be able to preserve their vitality for many years, even decades, that might otherwise have been compromised by chronic disease. Many challenges remain, but our work is showing that it may be possible to create a future where a longer life is synonymous with a better one.

A gateway to prevention

Fundamentally, healthspan medicine is about determining where each person is on their health journey



Fundamentally, healthspan medicine is about determining where each person is on their health journey and helping them improve their trajectory.

and helping them improve their trajectory. First, it is necessary to establish current health status as comprehensively as possible. We introduce the patient to the concepts of healthspan medicine through a "gateway experience", which includes extensive evaluation.

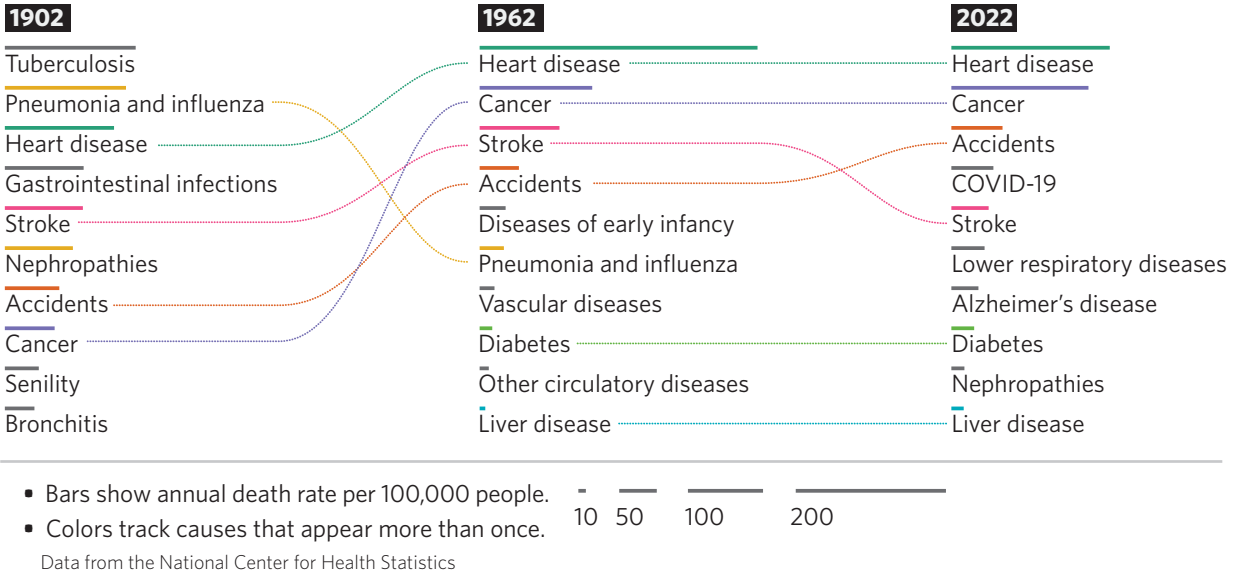
Ideally, a single clinical site would have all necessary equipment and personnel to carry out the gateway experience in a single day, though this isn't essential. This gateway day collects essential patient information and has a strong psychological and emotional impact—it marks the beginning of a lifelong journey. Afterwards, we follow up with regular coaching and biomarker updates. These provide ongoing support and metrics to evaluate progress and monitor for early signs that could lead to disease.

At the foundation of healthspan medicine are the pillars of health. These are easily understood through four simple verbs: eat, move, sleep and connect. These words encompass the ideas that nutrition and diet, which include eating healthy food in the right amounts; getting regular physical exercise and quality sleep; and maintaining balance through mindfulness and human relationships, are all necessary for optimal health. These fundamental lifestyle factors currently offer the greatest opportunities to expand healthy longevity and delay disease.

Many primary care clinicians recognize how important these pillars are to their patients' health and well-being. But doctors are often reluctant to advocate lifestyle changes because they're considered too hard to act on. When doctors do address them, they generally give fragmented, outdated and one-size-fits all recommendations. In a rigorous healthspan medicine practice, doctors and coaches evaluate these pillars with a combination of patient-reported information, physiological biomarkers, functional assessments and wearable devices for continuous monitoring. They identify opportunities for improvement and develop a personalized health optimization program.

Effective healthspan medicine relies on regular feedback to the patient, which empowers and encourages self-determination. In our experience, this works best with a team that includes a medical professional, the patient and at least one coach or advocate—a new type of healthcare professional called the healthspan coach. At Optispan our healthspan coaches are trained in the principles and practices of health optimization. They have a working knowledge of systems medicine, geroscience principles and the

Top Causes of Death in the U.S.



pillars of health. They are informed about, and empowered by, the best technologies available to support behavior change, such as artificial intelligence tools. Coaches provide regular feedback, encouragement, and strategies that support long-term health-promoting behaviors.

A systems medicine approach

Rather than focus on individual diseases in isolation, healthspan medicine relies on a systems biology framework to understand how the human body can function optimally. It considers health to be the balanced coordination of interconnected organs, tissues, and cells. For simplicity, these are often categorized based on functions, such as cardiovascular, gut, hormonal, immune, skin, respiratory, and musculoskeletal. Understanding how they interact with each other and using biomarkers—molecules that indicate how biological systems are functioning—allow us to detect early perturbations that might knock an individual's health trajectory off course (see "A Return to Holistic Medicine" on page 18). These perturbations often suggest some corrective action we might take. In this way, we can identify each person's highest risks and monitor the progress of mitigation strategies.

Geroscience, the scientific discipline linking biological aging with age-related functional declines, informs much of healthspan medicine. Major advances in geroscience over the past two decades have identified key mechanisms of aging, which have been formalized into twelve hallmarks (see 'What Drives the Aging Process?' on page 27), along with a growing understanding of the molecular networks that underlie, connect and regulate these hallmarks.

In recent years, new technologies have allowed for the development of high-dimensional molecular signatures of biological aging, or "clocks," that appear to correlate with individual disease and mortality risk. While useful as research tools (see 'How Old Are You Really?' on page 32), clinical application of so-called biological aging clocks, particularly those marketed direct-to-consumer, should be approached with caution to avoid confusing patients and inducing unnecessary anxiety. In our experience, current biological age assessments may provide useful insights when used in combination with more established biomarkers, but they are not yet sufficiently validated for mainstream application.

The most effective approaches to slow biological aging are tightly coupled to the pillars of health (nutrition, exercise, sleep, and connection). Estimates suggest that many people can gain more than a decade of healthspan simply by improving their pillars. There is also growing interest in drugs or supplements that can potentially mimic, or enhance, these lifestyle approaches. Preclinical studies have identified several "gerotherapeutics"—drugs that increase lifespan and healthspan in laboratory animals. Some with indirect evidence for potentially similar benefits in humans. As a result, a small but growing number of practitioners are specializing in off-label prescriptions for putative 'longevity' therapies such as rapamycin, metformin, SGLT2 inhibitors and other drugs.

Two additional classes of therapeutics worthy of mention here are hormone optimization strategies and GLP-1 anti-obesity drugs such as Ozempic, Wegovy, and Mounjaro. These have seen a surge in popularity and a corresponding increase in the number of providers who are willing to prescribe them, including many who have co-opted the phrase "longevity medicine" without any real background knowledge or training in the field. While there is evidence that these therapies, when used properly, can enhance healthspan for many people (and perhaps even slow biological aging itself), there is also the potential for harm. For example, many patients lose significant muscle mass and bone density from GLP-1 agonists when prescribed in isolation, placing them at higher risk of frailty and potentially counteracting benefits attained in other domains. Such negative outcomes are largely preventable when use of these medications is approached through the framework of a holistic healthspan medicine program.

The most effective approaches to slow biological aging are tightly coupled to the pillars of health: nutrition, exercise, sleep and connection.

It is important to recognize that off-label use of pharmaceutical or natural products to slow biological aging is currently highly speculative. Their risk-versus-reward profiles are evolving with new data, and few definitive biomarkers are available to evaluate individual efficacy. Given the growing appetite for access to these therapies, there is an urgent need to develop validated biomarkers and expert guidelines to help responsible practitioners in best meeting the needs of their patients.

Opportunities and challenges

Widespread adoption of healthspan medicine has the potential to give most Americans 10 to 20 years of additional high-quality life. The social and economic dividends from recovering these lost decades are enormous. Indeed, a recent estimate from the McKinsey Health Institute calculated that for each year of increased healthy life, the U.S. would see $38 trillion in economic gain. While some will claim this kind of care is only for the rich, applying only a fraction of these gains would be sufficient to provide top-tier healthspan medicine to every man, woman, and child in the U.S.. For this to happen, however, at least two significant barriers must be overcome.

First, incentive structures will need to change to encourage aggressive preventative care. Such a change will require insurers, administrators, and policy makers to recognize that keeping people healthy is ethically and economically superior to keeping people sick. In this regard, healthspan medicine is not a replacement for reactive disease care and need not threaten entrenched interests in the health care industry. Even with optimal prevention, people will still get sick. Yet, because healthspan medicine often detects problems early on, it provides opportunities for more effective treatments to halt or even reverse the trajectory of disease. This has the potential to alleviate stress on hospitals providing acute care and reduce the enormous burden of chronic disease.

Second, responsible stakeholders must align on a core set of values, standards and best practices. While a growing number of practitioners are embracing many of the concepts of healthspan medicine, the field remains fragmented and quality of care is uneven. Unfortunately, some self-identified longevity medicine providers prioritize cosmetic treatments, unproven experimental procedures, or excessive reliance on supplements over evidence-based approaches grounded in rigorous science. Adding to the challenge, misinformation from online personalities and direct-to-consumer companies promoting questionable products has fueled skepticism and undermined trust in the field. To move forward, it is imperative that practitioners commit to ethical, transparent, and science-driven practices. By fostering collaboration, self-regulation, and accountability, the healthspan medicine community can elevate its credibility and unlock its potential.

We have an extraordinary opportunity to transform the quality and quantity of life for millions of people using the tools and knowledge available today. By reaching a consensus on protocols and approaches rooted in rigorous science and clinical best practices, the field of healthspan medicine can inspire confidence among patients and the broader medical community. As this vision takes shape, healthspan medicine has the potential to become a cornerstone of modern healthcare—ensuring that longer lives are not just possible, but also vibrant and fulfilling. With collaboration, innovation, and a shared commitment to proactive care, we can create a future where everyone has the opportunity to thrive at every stage of life.

Matt Kaeberlein is CEO of Optispan.

How Old Are You Really?

Biomarkers of aging are revealing important insights into health and longevity

BY MORGAN LEVINE

ILLUSTRATIONS BY MYRIAM WARES

How old are you?

It's a seemingly simple question, yet at the same time complex, with an air of intrusiveness and impropriety. Most of us will give a straightforward answer: the number of years that have passed since our birth.

In many ways, however, this question signifies something more than a query about your time on Earth. It elicits something about your state of being, your health, and unfortunately for some, even your status and value in society. We attach meaning to ages like 65 or 100 and even consider a person's age when assessing their suitability for a job, like president of the United States.

In reality, time is not what gives age its significance. Instead, it is the underlying biological process that changes over time. That process can take a robust and resilient body and transform it into a state of frailty, dysfunction and, eventually, death.

To date, no human has ever escaped this process, yet some scientists and longevity gurus have suggested its inevitability is up for debate. Some scientists believe that we may one day discover an intervention capable of transforming our biology—allowing years to pass with wisdom gained and experiences lived but without bodily degeneration. This possibility assumes that time and the biological process we call aging are separable. To break the bonds that currently link time and aging, scientists first need new ways to measure the process of aging, rather than merely counting our trips around the sun.

That's where biological age comes in. The concept dates to the 1950s when British biologist, Peter Medawar declared the need for an agreed-upon system of measurements for what he, at the time, termed "senescence." Nearly 70 years later, one might think we've achieved it. Many biologists, mathematicians and computer scientists have published papers detailing new models and equations claiming to quantify biological aging. Companies advertise their tests online, and influencers tout lifestyles and protocols that they claim to reverse biological age. The reality is less certain. While experts largely agree that the concept of biological aging is valid, they don't agree on how best to measure it.

Much of the challenge lies in the fact that biological aging is what statisticians call a "latent variable," which means it cannot be directly observed or measured. Instead, latent variables must be inferred mathematically from other measurements. This implies we will never measure it perfectly but instead will only generate fuzzy estimations of it. For example, we can precisely measure weight, blood pressure, chronological age and other observable variables. Latent variables such as intelligence, health, and biological age are abstract concepts that we will never be able to perfectly capture. (This is why people still argue over whether IQ tests provide good estimates of intellect.)

Not all hope is lost. Biological age estimates exemplify the maxim of 20th century statistician George E.P. Box: "All models are wrong, but some are useful." No model will ever provide an accurate read-out of biological age. That said, some current models can reveal important insights about your health and aging from a biological perspective.

Time is not what gives age its significance. Instead, it is the underlying biological process that changes over time.

So how do we judge the merit of something for which there is no ground truth to compare it? Our only solution is to come up with metrics, or benchmarks, to help us assess the degree to which a measure of biological age captures the underlying theoretical construct we are trying to estimate.

When assessing the validity of any model claiming to measure biological age, here are the criteria I and many other experts use:

Biological age should be loosely linked to chronological age. Because we can't directly assess biological age, we need to use other observable metrics. And since no one has yet to discover a way to indefinitely halt biological aging in people, any measure of it should increase as a function of chronological age. Measures of biological age that have weak correlations with chronological age—where it wouldn't be hard to find 80-year-olds with the same biological age estimate as 30-year-olds—are probably not valid. An example of a weakly correlated age estimate is measuring the length of telomeres (protective caps at the end of DNA strands that shorten over time) in white blood cells.

Conversely, measures that correlate so strongly with chronological age as to be indistinguishable are also not valid—we don't expect all 30-year-olds to

have the same biological age. Like Goldilocks, what we look for is a correlation that is strong, but not too strong. Most 60-year-olds, for instance, would have higher biological ages than most 50-year-olds, but they'd have a small range of predicted biological ages (say 10 years) among themselves.

Measures of biological age should signify something about the individual's function, disease risk and remaining life expectancy. More so than chronological time, biological age should be associated with health and disease. Individuals with higher estimated biological age (compared to their chronological age) should be those who are indeed at greater risk of functional decline, adverse health events, and lower life expectancies. If measures do not predict these outcomes, they are likely capturing characteristics that change over time yet have no actual bearing on health and well-being—for example, the graying of hair. Similarly, behaviors or interventions that we know alter health outcomes should also alter any good measure of biological age, and those that do not affect health outcomes should not. For instance, exercise and a healthy diet are thought to be beneficial to the aging process and thus should be reflected in estimates of biological age.

Quantifying biological aging is challenging, yet meeting that challenge is necessary if we want to intervene to slow, stop, or even reverse aging.

Measures of biological age should be stable, but not too stable. We do not expect someone's biological age to fluctuate wildly over short periods. Moreover, if we were to estimate someone's biological age twice in the same day, we would expect to get the same answer. Unfortunately, many of the tests currently being used to quantify aging are rife with technical artifacts and noise, making them ill-suited for use in individuals (though they may be useful in population studies). For instance, in 2022 my team and I discovered that epigenetic clocks, the most popular methods to date for estimating biological age can produce estimates that differ by nearly nine years when measured from the same blood sample. (This method estimates biological age by interpreting methylation patterns in DNA from genes being turned on and off, which change as people age.) While we were able to develop statistical techniques to remove this noise, many estimates available don't correct for these artifacts and are therefore still at risk of delivering biased results.

Measures of biological age should reflect the multifactorial nature of the aging process. I immediately dismiss any estimate of biological age based on one metric alone—for instance, VO_2 max, glucose or lung capacity). Most lack the proper stability, or they fail to robustly predict bodily decline. Even if they do both, they are certainly painting an incomplete picture of an individual's overall aging process. While each of us can be defined by a single chronological age, we can't say the same about biological age. Every organ in our body, if not every cell, is likely aging at a different rate, and therefore has a different biological age. This explains why some people develop heart disease, yet maintain muscle strength, while others might experience cognitive decline, but enjoy prolonged metabolic health. The multifactorial nature of the biological aging process means that we will never adequately capture it using a single quantitative value. Instead, we need to work towards developing models that more fully encompass all the ways our bodies might fail us over time.

Science has shown that discovering biomarkers of biological aging is within our reach. In fact, with the arrival of advances in artificial intelligence and machine learning and the success of AI in domains like language and vision, many are now turning their sights to biology. Models are being developed to quantify and manipulate the states of molecules, cells, organs, and organisms, and eventually these powerful tools may uncover the keys to programming health.

Despite AI advances, biological age estimates will always have shortcomings. We will still have to be cautious in our personal pursuits of health to avoid over-interpreting biological age changes. Claims to have reversed biological aging should be examined critically, and individuals employing such metrics for their own longevity journeys should be mindful of concepts like Goodhart's law: "When a measure becomes a target, it ceases to be a good measure."

Morgan Levine, Ph.D., is a vice president of computation at Altos Labs. Prior to joining Altos, she was a ladder rank professor at Yale University School of Medicine.

MATTHEW ALLEN PHOTOGRAPHY

Years and Miles Fueled by Veggies

Mike Fremont was born in Cincinnati, Ohio, in 1922. He became an entrepreneur and an advocate of healthy diet and exercise.

He studied mechanical engineering at Yale, worked for utility companies and other industries in Pittsburgh and Boston before returning to his hometown in 1948 to start his own company, Torque, Inc., a supplier of industrial clutches and brakes.

Two weeks after the youngest of his three children was born, Fremont's wife died of a brain hemorrhage. To cope with his grief, the challenges of being a single parent, and the stress of owning a business, he started running. After work, he'd run across a nearby dam. "Sometimes, I'd run with one of my children, maybe holding hands," he says.

Since then, Fremont has run more than 60 marathons. In 2018, he ran a mile at the Drake Relays in Iowa in just under 14 minutes, setting a record for the 95-plus category.

Fremont was diagnosed with colorectal cancer at age 70. He declined surgery and instead switched to a vegan diet. It "killed the pains, and they never came back," he says. "That diet works for me. It's the best possible thing you can do." When the cancer returned two years later, he had the surgery.

In the fall of 2024, at age 102, Fremont was still running and paddling a canoe.

Source: Interviews

[INFOGRAPHIC]

How We Age

System by system, our bodies lose their youthful speed, efficiency and effectiveness BY KATIE PEEK

When we age, our scrapes don't heal as quickly, our movements elicit grunts, our twinges persist longer than they used to. Larger shifts can also degrade our ability to go about our daily lives, setting off a spiral of diminishing health. By understanding these changes, researchers hope to be able to keep people healthy, active and productive throughout their lives. Here's what tends to happen to our bodies as old age approaches:

SKIN loses the proteins elastin and collagen, which makes it less elastic, it loses fat cells, which makes it thinner, more transparent, drier and more prone to bruising. When it folds, it tends to stay creased—that is, wrinkled. It also becomes less sensitive to touch.

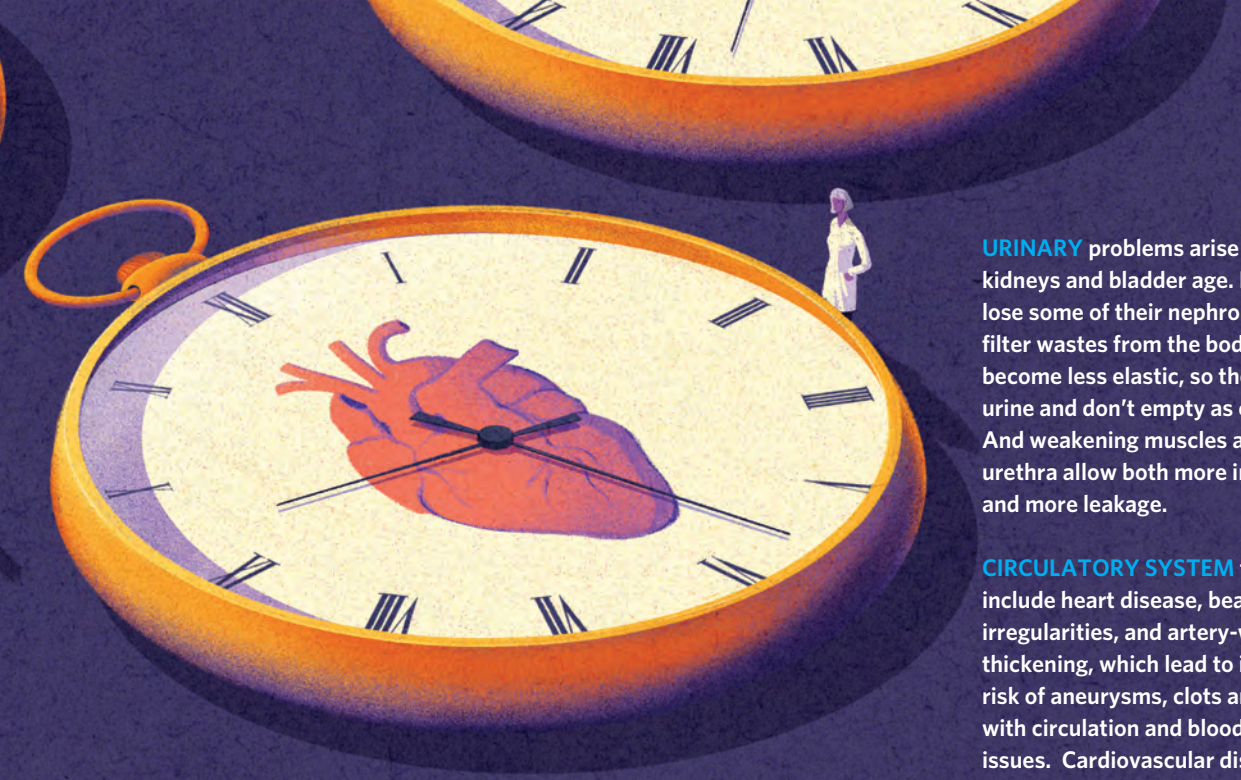
DIGESTION slows, which can make people more prone to constipation, gas, and reflux. The risk for colon cancer, ulcers and lactose intolerance rises. In general, however, the digestive tract is one of the body's most stable systems.

The **BRAIN AND NERVOUS SYSTEM** degrade significantly. Nerves transmit signals more slowly and can be impeded and pinched by hardening cartilage in the spine and joints. Reflexes slow down and short-term memory, verbal recall, and processing speed diminish.

EYES lose sensitivity. The pupil is slower to adapt to changing brightness, and the retina does not detect low levels of light as efficiently. The lenses grow stiffer and work harder to bring close objects into focus. Fewer nerves transmit data to the brain, so depth perception diminishes.

REPRODUCTIVE SYSTEMS age differently for men and women. Women experience the seismic shift of menopause, in which estrogen and other hormones drop to pre-menarche levels in a few years, lowering libido and making the vagina drier. In men, by contrast, testosterone levels drop gradually, affecting libido and virility.

MYRIAM WARES



URINARY problems arise as the kidneys and bladder age. Kidneys lose some of their nephrons, which filter wastes from the body. Bladders become less elastic, so they hold less urine and don't empty as completely. And weakening muscles around the urethra allow both more infections and more leakage.

CIRCULATORY SYSTEM failures include heart disease, beat irregularities, and artery-wall thickening, which lead to increased risk of aneurysms, clots and problems with circulation and blood pressure issues. Cardiovascular diseases are the leading cause of death.

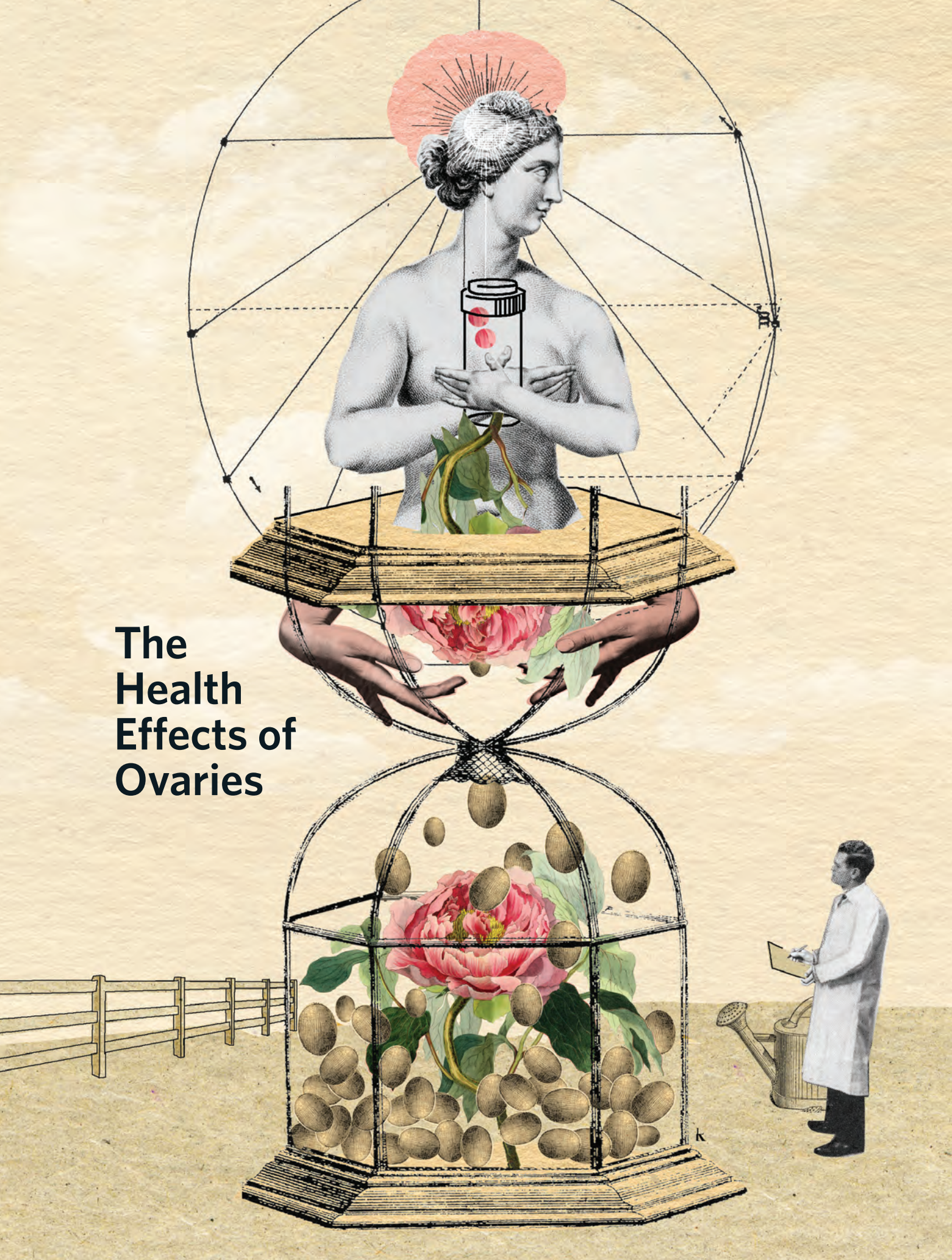
The **IMMUNE SYSTEM** quickly loses its ability to generate new T cells, important for fighting infection, in the first decades of life. After that, the body's 450 lymph nodes work to keep existing T cells healthy but lose effectiveness late in life. White blood cells and macrophages also weaken and slow.

HEARING degrades with exposure to loud noises, which can build into significant hearing loss. The loss is usually most pronounced with high pitches, which affects the ability to hear consonant sounds.

The **RESPIRATORY SYSTEM** holds up relatively well. But, the diaphragm can weaken, making breathing more difficult, especially during exercise. The lungs also become less sensitive, allowing foreign particles to build up before nerves trigger a cough to expel them.

BONES become less dense and more brittle, and diminished cartilage in the joints reduces their ability to absorb impacts. Osteoarthritis, a decrease in bone density that affects half the world's seniors, makes daily tasks more difficult and painful.

TASTE AND SMELL diminish somewhat after about age 60. Taste buds decrease in number and become physically smaller. (Sweet and salt flavors degrade more than bitter and sour.) Smell can disappear in the early stages of neurological disorders such as Parkinson's and Alzheimer's.



The Health Effects of Ovaries

Scientists must find a way to extend the benefits of healthy ovaries to women even after they pass menopause **BY FRANCESCA E. DUNCAN | ILLUSTRATIONS BY KATY LEMAY**

Women live far longer than they used to in the U.S., and five years longer than the average U.S. man. As a result, many believe that they're the healthier sex. But U.S. women actually spend more of their late lives in poorer health or frailty. In other words, their healthspan falls far short of their lifespan. And a lot of that comes down to their ovaries.

Ovaries, the female gonad, play a pivotal role not only in reproduction but also in overall health. They are responsible for producing eggs and endocrine hormones, including estrogen and progesterone, which are critical for maintaining the menstrual cycle. The effect of these hormones on overall health is apparent at the age of menopause, when ovaries stop working. Post-menopausal women are at heightened risk for conditions such as osteoporosis and heart disease.

Even though lifespans for women have increased to 80 in the U.S., the age of menopause has stayed more or less fixed at 52 years on average, which means women live for decades with a compromised endocrine system.

Because women spend more of their late lives in poorer health or frailty, the concept of healthspan must encompass the effect of the reproductive organs on women's health as they age. If the ultimate goal is to align healthspan with lifespan—to ensure that women stay healthy throughout their lives—scientists will have to find a way to extend the benefits of healthy ovaries to women after they have passed menopause.

A fast-aging organ

Aging is associated with a general deterioration of tissue function that underlies numerous chronic conditions and illnesses. The female reproductive system is unique in that it is one of the first in the human body to show overt signs of aging. Fertility begins to decline in women in their mid-30s, and reproductive function ceases completely at menopause. Reproductive aging is occurring in females in the prime of their life.

The ovary is the female gonad, which houses egg cells. Women are born with all the eggs they will ever have, and each egg is surrounded by supporting cells within a follicle—the functional unit of the ovary. A major hallmark of ovarian aging is the loss of egg quantity.

Primordial follicles, formed in the womb, make up the ovarian reserve, which is finite and nonrenewable. The ovarian reserve naturally declines across a female's reproductive lifespan. Females have about a million primordial follicles at birth and a few hundred thousand at puberty. By menopause, only about a thousand primordial follicles remain. Many factors can accelerate the natural age-dependent trajectory of follicle loss—genetic conditions such as X-chromosome abnormalities; smoking and environmental contaminant exposures; and medically induced treatments such as chemotherapy and radiation.

The female reproductive system is unique in that it is one of the first in the human body to show overt signs of aging.

As the number of egg cells drops, the quality of the eggs that remain also decreases. For example, the incidence of chromosomal abnormalities, or aneuploidy, in eggs from women of advanced reproductive age increases dramatically. These abnormalities manifest when the cell undergoes final stages of maturation prior to ovulation. A recognized example of this phenomenon is trisomy 21, or an extra copy of chromosome 21, which results in Down syndrome. The likelihood of having a child with Down syndrome increases significantly in women as they age.

Although a multitude of mechanisms contribute to the decrease in egg quality with age, many are related to the fact that the egg is an extremely long-lived cell. Eggs are formed in utero during fetal development, but are not ovulated until decades later, between puberty and menopause. By then, like a car parked outside through countless winters, the egg is vulnerable to accumulation of damage.

The precise relationship between egg quantity and quality is not completely understood, but it is possible that they are intertwined. As follicles grow, they produce and secrete signals that positively influence the growth and development of nearby follicles. As the number of follicles declines with age, so do the levels of these important signals.

Rising risk

The decrease in both egg quantity and quality together contribute to adverse clinical outcomes. For example, women of advanced reproductive age are at a higher risk of infertility and may need to rely on medically assisted reproduction to conceive. Furthermore, even if women in this age group can conceive on their own, they are at higher risk of spontaneous abortion or are more likely to have twins. They are also at increased risk of complications during pregnancy or having offspring with congenital defects. As more women globally delay childbearing, the negative effect of aging on fertility is having tangible societal consequences, such as more difficulty achieving and maintaining pregnancies and greater prevalence of birth defects. The age at first time birth of women in the U.S. has increased from 25.6 years in 2011 to 27 years in 2024, and this upward trajectory is not only continuing but is a record high.

Although reproductive aging occurs in males and can have measurable impacts on the health of sperm and epigenetic effects on the next generation, the male reproductive system ages more slowly than that of females. For example, the likelihood of a woman being able to conceive without medically assisted reproduction after her mid-40s is exceedingly rare. In contrast, men have been reported to father children into their 90s.

Infertility in general can have profound effects on quality of life and well-being. Women are at a distinct disadvantage to men as they face the biological realities of a reproductive system that ages at what is often considered to be the prime of life. As a physician in obstetrics and gynecology once noted, the ovaries reach their peak potential long before their first use.

The impact of female reproductive aging is much broader than fertility. As the follicles containing eggs grow and develop in the ovary, they produce and secrete estrogen and several other hormones. Estrogen is a steroid hormone that regulates reproductive organs and sexual health. It also controls multiple downstream organs, including the brain, heart, skin, musculoskeletal system and immune system. The loss of follicles with age causes estrogen levels to drop, which can have a plethora of effects on overall health. For example, low estrogen levels can result in bone loss and osteoporosis, as well as increased risk of atherosclerosis and cardiovascular disease.

Medical interventions and health advances are fundamentally changing the way women live. Although the age at which women reach menopause has stayed constant for several centuries, lifespan has been extended significantly. Only 100 years ago, the average lifespan for women in the U.S. was approximately 55 years; it is now 80 years. (Average life expectancy of men in the U.S. is 74.8 years.) This means that women are living nearly three decades with the altered endocrine environment and negative general health consequences of reproductive aging, even though menopause is a part of normal physiology and not a disease.

There appears to be a relationship between menopause and life expectancy: premature menopause is associated with shorter life expectancy and later menopause with longer life expectancy. The ability to extend reproductive function beyond midlife would better align childbearing years and overall healthspan with current longevity.

Infertility in general can have profound effects on quality of life and well-being.

Extending ovarian function

Age-related infertility is primarily rooted in defects that occur at the level of the egg, instead of other organs such as the uterus, according to large-scale data from medically assisted reproduction and specifically in vitro fertilization. Conceiving and giving birth to a child carries a strong maternal age effect, meaning that the risk of complications increases when eggs come from an older woman.

The biological age of the egg is critical in reproductive outcomes. If a woman in her forties undergoes medically assisted reproduction with her own eggs to conceive, it is highly unlikely that she will take home a baby. However, if a woman instead uses donor eggs from a young healthy woman (typically in her 20s) to conceive, the chances are far higher. These observations support the use of planned fertility preservation, or egg freezing, at a younger age with the intent of using them later. But this approach only addresses fertility, not the endocrine function of the ovary. It does not eliminate the inherent pregnancy risks in older individuals and is not a guarantee of future parenthood.

Reproductive longevity can also be extended with hormone replacement therapy (HRT), designed

primarily to manage symptoms of the menopausal transition. HRT involves administration of supplemental estrogen and sometimes progesterone, which the ovary no longer produces at sufficient quantities. HRT reduces common perimenopausal symptoms, such as hot flushes, vaginal dryness, mood swings and sleep disturbances. However, HRT is a weak substitute for a pair of healthy ovaries. Estrogen replacement does not address fertility. It is generally not prescribed for long-term use due to potential increased risk of breast cancer and cardiovascular disease. And it leaves out the other ovarian steroid hormones, including androgens, and myriad nonsteroidal hormones, such as activin, inhibin, follistatin and anti-Müllerian hormone, as well as growth factors. Furthermore, it is not clear whether the steady hormone levels achieved during HRT are an adequate substitute for the dynamically fluctuating levels of hormones characteristic of natural ovarian cycles.

KATY LEMAY

Emerging strategies

Because of these limitations, we clearly need better, more holistic therapeutic interventions that address both fertility and endocrine function. One potential strategy is to delay reproductive aging by preserving ovarian tissue. The idea is that women would remove and freeze a portion of their ovaries at a young age. The ovarian tissue that is left in the body can compensate for what was removed. We know this because women who have one of their ovaries removed do not undergo menopause appreciably earlier than women with both ovaries intact. As women approach perimenopause, they would then thaw their cryopreserved tissue and have it transplanted back. This method was originally developed for women undergoing fertility-threatening treatments for cancer and other diseases. Hundreds of babies have been born as a result of this procedure. The transplanted ovarian tissue can sustain endocrine function for several years, and ovarian function can be maintained for longer periods with repeated transplants.

Although potentially an attractive option for extending reproductive longevity, this strategy requires an invasive surgical procedure. Ovarian tissue cryopreservation is an acceptable fertility preservation technique for cancer patients, according to guidelines of the American Society for Reproductive Medicine, but using the procedure to extend reproductive longevity in healthy individuals requires further research.

Another attractive target for sustaining ovarian function is the tissue microenvironment—the "nest" in which eggs develop. Several years ago, my laboratory discovered the importance of the microenvironment in which the follicle develops and how it changes with age. When we isolate mouse follicles and eggs from the ovary for research purposes, we poke the ovaries with needles under a microscope. We found that it was more difficult to isolate follicles from ovaries from old mice compared to young ones because the tissue was physically tougher.

This observation reminded us of fibrosis, a biological process characterized by accumulation of collagen proteins that form a matrix or scaffold of tissues. Fibrosis is associated with inflammation, a natural reaction in response to infection or tissue damage. Fibrosis and inflammation are hallmarks of several aging tissues, including the lung, kidney and heart; if not properly resolved, tissue dysfunction ensues. When we looked into this phenomenon, we found that aging mouse and human ovaries tend to stiffen in the same way.

These changes in the aging ovary have significant implications for aspects of ovarian function, including follicle growth, egg quality, and ovulation. They may also have implications for how ovarian cancer develops, since cancer cells prefer to colonize stiff, collagen-rich tissues. Several research teams, including my own, have found in preclinical studies that drugs with anti-fibrotic properties can improve reproductive function and longevity. By administering drugs that reduce fibrosis, we can maintain the quality of the ovarian microenvironment, or nest, and prevent key age-related changes in ovarian function both at the level of the egg and endocrine function. These findings are laying the foundation for early-phase clinical trials in women, hopefully in the next few years.

Strategies to improve ovarian function in women beyond middle age raises many questions. Would women want to extend their healthspan if a potential consequence was also extending their childbearing years? Will women who choose to have children in their 50s or 60s and beyond have to deal with age-associated pregnancy risks, or will improved healthspan negate such concerns? How far can we push reproductive longevity? Because women are born with a finite ovarian reserve, there presumably will be a limit to how long ovarian function can be extended, but what is that end point? Could sustained physiological levels of ovarian hormones eventually have negative health consequences? Since the prospects for extending reproductive longevity are likely to occur in our lifetime, we must be prepared to address these safety and ethical considerations.

A priority on health

As drugs are developed that target the mechanisms of aging to prevent age-related conditions and diseases, these therapeutics may not have the same efficacy in both sexes because of unique underlying biology.

The biology of males and females, driven in part by unique sex hormones and X and Y chromosomes, are different at the level of molecular and cellular mechanics. As a result, the same organs may age differently in males and females. This translates into sex differences in age-related diseases. For example, women have a higher incidence and increased death rates compared to men from Alzheimer's disease and dementia, hypertension and other types of heart disease, chronic obstructive pulmonary disease and kidney disease. Women also have more vision impairments, worse respiratory function and reduced muscle strength and physical performance.

The biology of males and females, driven in part by unique sex hormones and X and Y chromosomes, are different at the level of molecular and cellular mechanics.

Because research findings on one sex are not typically representative of all, preclinical studies aimed at extending healthspan must include both male and female model organisms. Sex differences may also impact the way drugs work, a fact that will be imperative to acknowledge once compounds enter clinical trials. For example, females are more likely than males to experience adverse drug reactions.

Reframing the discussion of healthspan to include reproductive and women's health raises new questions and offers new opportunities for growth and discovery. Can signals released by the aging ovary set off a cascade of aging across tissues in women? Are the mechanisms of reproductive aging conserved across tissues? Could reproductive health serve as a biomarker—a canary in the coal mine—for overall health.

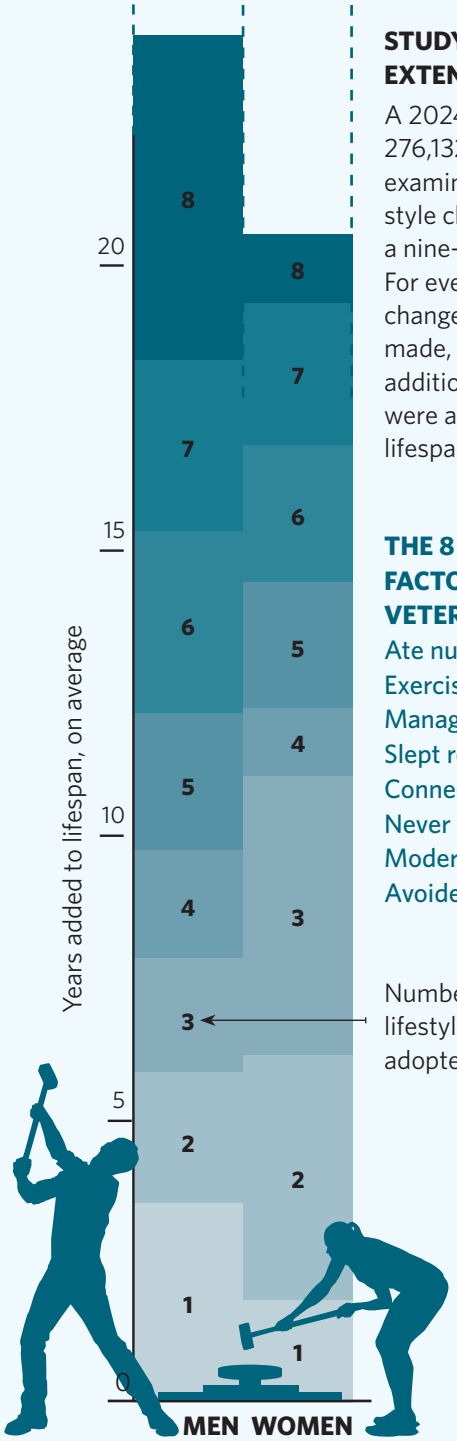
How women's reproductive organs age encompasses nearly all of the biological characteristics of aging overall. We clearly have a lot to learn from ovaries.

Francesca E. Duncan, Ph.D., is associate professor of obstetrics and gynecology at the Feinberg School of Medicine at Northwestern University and associate professor in residence at the Buck Institute for Research on Aging.

[INFOGRAPHIC]

The Lifestyle Changes That Increase Healthspan

Want to increase your own healthspan? The genetic die may be cast, but it's still possible to add healthful years with lifestyle changes. Two of recently published studies, one on U.S. veterans and one on U.K. civilians, helps quantify by how much. Each study monitored nearly 300,000 people over a decade, tracking their lifestyles and looking for payoffs to healthy habits. The takeaway: small changes can have big effects, and big changes can have huge ones. **By Katie Peek**



STUDY 1: EXTEND LIFESPAN

A 2024 study of 276,132 U.S. veterans examined eight lifestyle changes over a nine-year period. For every additional change a person made, statistically, additional years were added to their lifespan.

THE 8 LIFESTYLE FACTORS IN THE VETERAN STUDY:

Ate nutritiously
Exercised
Managed stress
Slept restfully
Connected socially
Never smoked
Moderated alcohol
Avoided opioids

Number of lifestyle changes adopted

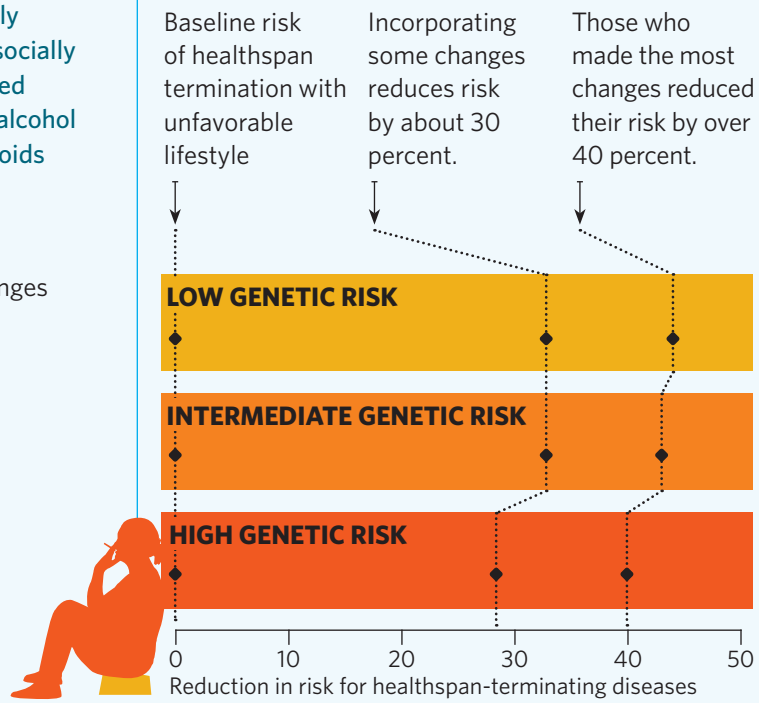
STUDY 2: INCREASE HEALTHSPAN

People who adopted healthy lifestyles also saw longer healthspans, according to a 2023 study of 288,359 U.K. residents. The healthspan increased whether or not the person had a genetic predisposition to what the researchers called "healthspan-terminating events."

THE 5 LIFESTYLE FACTORS IN THE U.K. STUDY:

Ate nutritiously
Exercised
Kept off excess weight
Never smoked
Moderated alcohol

The U.K. study participants were divided into groups according to their genetic predisposition to diseases and conditions that tend to shorten healthspan, such heart disease and certain cancers.



The Doctors of Medicine 3.0

By incorporating healthspan into clinical practice, some doctors are navigating a gray area between mainstream science and more speculative therapies

BY ADAM PIORE | PORTRAITS BY MONICA HELLSTRÖM

MICHAEL AUSTIN

George Haddad had some alarming news for his new 34-year-old patient. After taking a blood sample, the Seattle-based longevity doctor had run a trio of biomarker tests designed to measure his client's "biological" age: The patient had the blood of a middle-aged man.

"He looked like he was in his 40s," recalls Haddad, an M.D. specializing in internal medicine and cofounder and chief medical officer of Optispan, a Seattle-based healthspan technology company that operates a brick and mortar clinic with a telehealth option. "When we did the testing on him, he was consistently 10 years older across the board."

Haddad is part of a growing cadre of doctor-entrepreneurs who are embracing a new healthcare paradigm with a tantalizing promise: that by taking certain actions, it may be possible to reverse aging, live longer, and extend a state of disease-free living almost until the very end. Those actions range from eating more broccoli to consuming experimental medications.

Peter Attia, a best-selling author and podcaster, calls it "Medicine 3.0." His Austin, Texas-based longevity clinic serves celebrity and high-net worth clients willing to pay into the six figures for his services.

Medicine 2.0 refers to practices of the past few centuries up to the present. (Medicine 1.0 refers to the days when doctors didn't necessarily know anything about science.) According to Haddad, Attia and other longevity doctors, Medicine 2.0 is based on an antiquated approach that is fundamentally defeatist: wait for things to break, and then try to pick up the pieces. It might have made sense in the 19th century, when our understanding of the human body was primitive and the tools we had to measure and characterize human biology and change it were crude or nonexistent. But thanks to a revolution in molecular biology and a slew of technologies, it no longer has to be that way.

In recent years, researchers have made dramatic progress unraveling the mystery of aging, homing in on cellular processes that go awry as we get older and fuel the negative spiral that ultimately leads to the body's systemic collapse. Many of the doctors who practice this kind of medicine are quick to take what's been found in the lab and bring it into the doctor's office, so patients can make use of it in their daily lives.

Those who do so make no apologies. Their argument goes something like this: the traditional medical establishment is constrained by a conservative "do no harm" approach that fails to account for a fundamental truth: doing nothing in the face of growing scientific evidence—even if it is not yet fully validated—constitutes an action of sorts. And doing nothing can sometimes cause more harm than acting on the best available evidence.

"We can tell you whether you're younger or older than your chronological age."

—GEORGE HADDAD

Most of what goes on in the offices of Medicine 3.0 doctors is based on solid, mainstream science. But not all of it. Sometimes doctors make recommendations based on science that is preliminary, meaning further study is needed to confirm its safety and effectiveness or proper dosing—or reveal it to be bogus. Doctors who practice Medicine 3.0 walk a tightrope between mainstream science and exciting new findings in the lab that, as promising as they are, have not been rigorously tested.

This approach presents something of a quandary to the average person hoping to take advantage of the emerging science of healthspan, which seeks to extend health into old age as much as possible. For them, the central challenge is to figure out whether their doctor can operate on the frontiers of medicine while maintaining the proper balance between risk and reward. For that, it helps to have an idea of what's risky and what's not.

Testing, testing, testing

The Medicine 3.0 experience usually begins with extensive testing. The methods of testing, like the interventions that follow, fall along a continuum of respectability. On one side are long-established, widely used tools that have long been accepted in the medical community. On the other side are tests that can be speculative and experimental.

Haddad usually begins with a DEXA, or dual X-ray Absorptiometry, scan, a body composition test that uses X-ray beams to measure the amount of fat, lean tissue, and bone in the body. He also uses blood tests to evaluate nutritional status and hormone levels. Then, using big data, he can compare those results to healthy norms and identify places to intervene. Is the client deficient in vitamin D, omega-3 or vitamin B_{12}? What about levels of estrogen and progesterone, testosterone, insulin and cortisol? These are all widely accepted tools.

Less widely accepted are the biological aging tests Haddad applied to that 34-year-old.

Those tests are based on recent discoveries characterizing a number of biological changes that are associated with a decline in cellular function and that can accelerate physical decline. For instance, as we get older, certain genes get turned on or off through a process known as methylation in ways that can interfere with healthy gene regulation, which in turn can interfere with the production of proteins we rely upon to keep our cells healthy. For example, abnormal methylation patterns can lead to cancer by suppressing the activity of tumor suppressor genes. Abnormal methylation has also been linked to cardiovascular disease, autoimmune diseases and nervous system disorders.

Then there is the phenomenon known as senescence. As we age, some cells stop dividing but do not die, entering an unhealthy zombie state. These senescent cells can lead to low-level inflammation that suppresses normal mechanisms of cellular repair and creates a toxic environment for neighboring cells. And in the aging process, proteins interact with one of several forms of sugar, in a process known as glycosylation, in ways that modify their structure and function and that can serve as biomarkers. The biological tests aim to measure these changes.

As we age, cellular methylation patterns and glucosylation change in predictable ways, and senescent cells accumulate, as demonstrated in large-scale longitudinal studies, including the Framingham Heart Study, the Dunedin Study and the Baltimore Longitudinal Study of Aging. "Based on that," says Haddad, "we can tell you whether you're younger or older than your chronological age."

Tests for these and other measures of biological aging are already being commercialized. (See 'How Old Are You Really?' on page 32.) A number of direct-to-consumer tests can characterize methylation patterns and glycosylation. Tests to measure senescence are harder to find, but they exist. Optispan, for instance, uses an experimental test produced by a North Carolina company to measure T cell senescence.

Attia, for one, is skeptical of these biological aging tests, mainly because they have not been sufficiently validated. For instance, some Medicine 3.0 doctors use the Horvath clock test to assess the biological age of patients. Former UCLA geneticist Steve Horvath, who pioneered the measure of methylation patterns as a proxy for cellular aging, developed the test as a research tool. Attia insists that the test is not informative for individual patients and does not belong in the doctor's office. "If you tell me that your birth certificate age is 65, I have a much better sense of saying, yep, I expect you to live about another 20 years," he says. In general, tests for biological age are "not even close to ready for prime time."

"We've gotten ourselves into kind of a bad spot in modern western life."

—KARA FITZGERALD

Haddad disagrees: "I can tell you from experience, these tests aren't perfect, but there's something there."

The four pillars and the Western lifestyle

Once they assess their patients, almost all doctors who practice Medicine 3.0 begin with the basics, focusing on optimizing their diets, sleep habits, stress-reduction techniques and emotional well-being. There is nothing speculative about the benefits of these interventions—primary care doctors often give the same advice. The difference is that Medicine 3.0 doctors put an emphasis on these steps as a way to prevent disease.

A key part of the Optispan approach, for instance, is a focus on "creating intentionality" around improving what Haddad calls "the four pillars of health: eat, sleep, move and connect." These are similar to Attia's four pillars of longevity (a balanced diet, regular physical activity, quality sleep, and strong social

MONICA HELLSTRÖM

connections). That's why Haddad's initial prescription for that middle-aged 34-year-old wasn't particularly revolutionary and did not require fancy testing. A quick medical history revealed that his client was sedentary and rarely exercised, had poor sleep habits, and was depressed, anxious and isolated. His diet consisted largely of processed junk food. "In his case, we didn't go to medicines," says Haddad. "For him, sleep was the low hanging fruit. So, we worked very hard on sleep hygiene."

Haddad also put his client on what he calls a "whole food challenge." Bread, rice and pasta were out. Vegetables, fish, eggs, and meat were in. By the time the 30-day challenge ended, he'd already lost 10 pounds and his blood sugar and lipids looked better. "If you just stop eating junk food, your biomarkers do improve," Haddad says. "That's not radical news."

For Kara Fitzgerald, who runs a Connecticut-based clinic focused on longevity and improving healthspan, everything starts with lifestyle. She is a prominent voice in the field of functional medicine, in which doctors take a holistic approach to their patients, taking into account nutrition, exercise, genetics and other factors.

Beyond the basics

Beyond the tried and true pillars of diet, exercise and sleep hygiene and social connection, which have broad mainstream acceptance, there are still plenty of interventions that longevity doctors can prescribe.

Unregulated supplements have some degree of support in the medical community. No one disputes that probiotics and phytonutrients aim to add compounds that are known to be good for the body, but there is a lack of clinical data to establish that when they are consumed as supplements, rather than as a part of normal food, they will survive the human digestion system and liver metabolism in a form that will allow them to actually get to where they need to go to have an impact. Furthermore, since they are not regulated by the FDA and often sell so well their promoters have no incentive to test them further, they lack the rigorous double-blinded studies needed to validate them.

Fitzgerald, like many longevity doctors, prescribes supplements, and in 2021 she published the results of a small randomized controlled clinical trial in 43 healthy adult males between the ages of 50 and 72 in the journal *Aging*. It showed that a simple 8-week treatment program of modifications to diet, sleep, exercise, along with supplemental probiotics and phytonutrients, chemical compounds found in plants like beta-carotene believed to have antioxidant properties, and meditation, was associated with a 3.23 year reduction in biological age, as measured by the online Horvath clock test—results not seen in a control group.

Longevity doctors are also focusing on fixing hormonal imbalances. A large percentage of people have hormonal imbalances caused by aging, and they've been exposed to environmental toxins, says Matt Kaeberlein, CEO of Optispan. Fixing those imbalances with hormone replacement therapy, he says, can make a big difference for a lot of people.

"Everybody in their 50s should be getting comprehensive hormonal tests at least once every few years to figure out where you're at," says Kaeberlein. "My view is if you need to get it fixed, get it fixed."

"Everybody in their 50s should be getting comprehensive hormonal tests at least once every few years to figure out where you're at."

—MATT KAEBERLEIN

Kaeberlein also suggests everybody get a DEXA body composition test every two to three years, starting in their 50s and possibly even earlier, aimed at measuring bone density, fat and muscle mass. "If you catch osteopenia and osteoporosis in your 40s, you're going to be in a much better place in your 60s and 70s than if you don't catch it and you fall down and get a hip fracture," he says. "These are pretty easy to fix, if you know need to fix them."

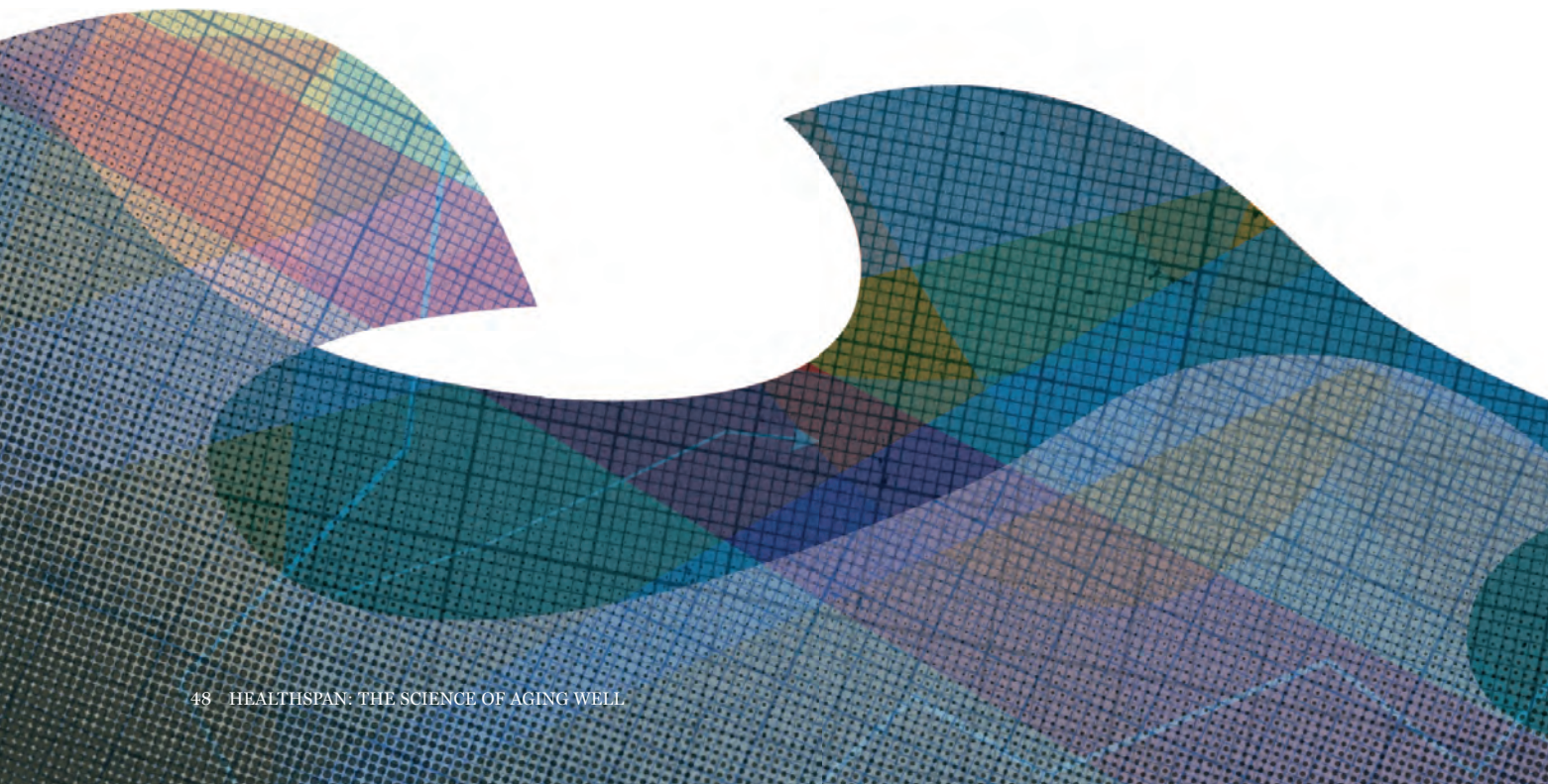
Prescribing boldly

Beyond the four pillars and beyond hormones and supplements lie the more controversial areas of longevity medicine, where doctors prescribe experimental medicines designed to hack the biology of aging—such as rapamycin, metformin, and drugs aimed at modulating nicotinamide adenine dinucleotide (NAD), an organic molecule that plays a key role in cellular metabolism and energy production. Some of these drugs are more speculative and riskier than others. While rapamycin and metformin are approved for other uses, and have plenty of safety data behind them, some treatments, such as stem cell therapies or plasma infusions, are so experimental many doctors won't touch them.

For those patients willing to engage with more experimental interventions, there are plenty of options. Perhaps the most widely prescribed of the experimental anti-aging drugs is the off-label use of rapamycin, a drug that mimics the effects of calorie restriction by hacking the pathway that regulates metabolism and cell division. The drug is approved as an anti-cancer therapy and to inhibit organ rejection in transplant patients. It has also been shown to extend lifespan in a wide array of animals, including worms and mice, and evidence is growing that it can have positive effects on dogs and humans.

Some scientists suggest that metformin, a diabetes drug used to lower blood sugar, may also protect cells from damage caused by unstable molecules known as free radicals and beneficial effects on blood vessel health that could extend life. Experimental drugs called senolytics, designed to remove senescent cells, are promising enough to be the subject of a $125-million, five-year NIH grant program. So far, they have shown some promise in clinical trials. Also in the mix are a host of other drugs designed to modulate levels of nicotinamide adenine dinucleotide, a molecule that helps the body convert food molecules into chemical energy, which decreases with age. Transdermal patches that deliver the molecule directly into the bloodstream of long COVID patients suffering from chronic fatigue are being used by a number of prominent clinicians. The treatments are designed to help the patients' mitochondria produce more energy. The results are promising, but so far anecdotal. A clinical trial to test their effectiveness is planned.

Much research remains to be done to prove the effectiveness of these drugs in people, proper dosing, drug interactions and, in some cases, safety. Since rapamycin and metformin are approved for other uses, they have enough clinical data behind them that the clinicians are confident they are safe. Both drugs, if



taken without doctor supervision, could be dangerous—in rare cases, metformin can cause a life-threatening condition called lactic acidosis and is usually not recommended for those with kidney disease.

In clinical trials, about five percent of patients taking rapamycin experience side effects sufficiently grave to stop taking the drug. The FDA also stamped the drug with a "black box" warning because of its potentially severe side effects. The drug can suppress the immune system—it has long been used to suppress the immune system in people who have undergone organ transplants and to inhibit cancer cell growth—which means users run a heightened risk of deadly infections.

Still, Kaeberlein considers the interventions relatively benign, as long as they're administered under a doctor's supervision. The lack of definitive evidence is not, by itself, a good reason to avoid them, he argues.

In longevity medicine, there's a need to act on ambiguous information, provided the medications don't carry big risks, according to the available science.

—SAJAD ZALZALA

The danger of caution

Haddad has not ruled out the use of drugs like rapamycin for his 34-year-old client. But he's more likely to prescribe it for someone who's already mastered the basics of self-care, as he did for a woman who came into his office one day. His impression was that she was in her mid-50s, which tests of her biological age confirmed. But the age on her driver's license—her chronological age—was 65.

"She was someone that had everything dialed in," he says. "She was eating an extremely healthy diet, exercised every day. Sleep wasn't perfect, but it was good. She was a content 65-year-old who was working for fun and had lots of joy in her life. She's like, 'Well, I want to be even younger.' She was greedy. That's how some people are, which is fine." To fine-tune her, Haddad prescribed hormone replacement therapy. He is also considering using rapamycin, because she wants to push beyond simple lifestyle interventions, and Haddad says that the potential benefits of the widely used drug outweigh the risks.

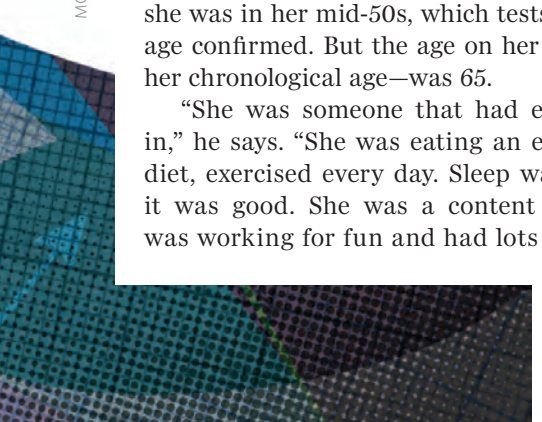
Haddad's clinical decisions with these two patients reflects Optispan's rethink of the "first do no harm" provision of the Hippocratic oath—the idea that doctors should, above all else, avoid harming patients. While this may be appropriate in cases where there are real dangers, Kaeberlein argues, the concept has been taken to such an extreme that it has made doctors overly cautious. And caution, when carried to the extreme, can itself be harmful.

"If you're stuck in the mindset of reactive disease care, you're always going to default to, well, we don't have the randomized clinical trials, so we shouldn't do anything," Kaeberlein says. "And I reject that viewpoint personally. I think that's a disservice to people." To gauge risk in longevity medicine, Sajad Zalzala, a family medicine doctor and founder of AgelessRx, a telehealth platform that serves 40,000 patients, says there's a need to act on ambiguous information, provided the medications don't carry big risks, according to the available science. (He steers clear of stem cell therapies.) The results for individual therapies vary widely by patient, and finding the right interventions can take experimentation and time, Zalzala says. But they are worth the effort, he says, since lifestyle inventions alone are unlikely to result in "extreme old age."

Medicine 3.0 doctors do agree on one therapy, which has zero side effects: placebo. "You can make a reasoned argument that if people take these things and suddenly feel better, even if it's not the active ingredient in the supplement," says Kaeberlein. "Is that a bad thing? I don't know. I mean, if it helps, it helps, right?"

Adam Piore is a science and health journalist, a longtime* Scientific American *contributor, and the author of two books.

MONICA HELLSTRÖM



Healthspan Coach

Peter Attia's best-selling book and podcasts have made him a popular source of practical advice for people who want to remain healthy longer

BY ADAM PIORE

ILLUSTRATION BY MONICA HELLSTRÖM

Peter Attia has been called a "longevity influencer," a "wellness trendsetter," and a "celebrity doctor."

Whatever the label, it would be hard to find a public figure with a hotter brand in the emerging area of healthspan and longevity science. His 2023 book, *Outlive: The Science and Art of Longevity,* marketed as a "groundbreaking manifesto" that challenges conventional medical thinking, has sold 1.5 million copies.

The 53-year-old physician, who trained at Stanford and Johns Hopkins, has become the popular face of the growing trend in medicine towards preventative measures

to extend the period of time people can live free of chronic disease. Through his company Early Medical, Attia practices what he calls Medicine 3.0, which entails quantifying and measuring the factors that can improve healthspan, including basic "blocking and tackling" like exercise, sleep and stress management, as well as off-label uses of longevity drugs like rapamycin.

Scientific American Custom Media's Adam Piore spoke with him about his own intellectual journey and what a middle-aged couch potato might do to remain spry until the minute he drops dead of old age.

SACM: Was there a moment when you realized that there was another way to look at medicine rather than just treating chronic disease after symptoms appear?

ATTIA: One of the first realizations, more than a decade ago, was that there's more to longevity than just living longer. Modern medicine tends to fixate on lifespan, but half of the longevity equation is on the healthspan side.

In reading the literature on centenarians, [I realized] that living longer is mathematically equivalent to delaying the onset of chronic disease. If you want to live longer, you have to make sure that if and when you get heart disease, cancer, neurologic disease, diabetes and so on, you get them much later than the average person.

Why has modern medicine done such a poor job on healthspan?

For me, it comes down to the definition. The modern system of medicine defines healthspan as the period of life that is free of disability and disease. But that's not really helpful. It's only when you clearly define and measure things that you have a hope of understanding how to improve them. In healthcare, what gets measured gets managed.

Healthspan can be broken down into three buckets: physical performance, cognitive performance and emotional health. Physical performance is going to come down to freedom from pain and certain metrics of strength, cardio, respiratory endurance, muscular endurance, peak anaerobic output, power, reactivity, flexibility, and balance. On the cognitive side, similarly, there are lots of very clear ways that you can measure things. Short-term memory, visual-facial memory, long-term memory, olfactory function, executive function, processing speed, crystallized intelligence, fluid intelligence. We have tests for all these things, so we can benchmark people and see what we can do to improve.

Emotional health would clearly be the least objective of the three, but it's certainly no less important. It comes down to happiness, a sense of purpose and quality of relationships.

> "For most of the things out there, the evidence is overwhelming that they have zero protective benefits whatsoever. It's a pretty short list of things that are really interesting."

Do you need a doctor to embrace healthspan medicine?

In many cases, it's going to be patient-directed. At some point, that person is going to have to merge with the healthcare system. So, for example, a patient says, "I need a doctor who's willing to check my aPob [a protein that plays a key role in the metabolism of the particles that carry cholesterol and triglycerides through the bloodstream]. And if it needs to be adjusted, I might need pharmacology."

How would you recommend finding a doctor willing to practice this way?

I would ask the doctor you're considering point blank, what is your approach to Medicine 3.0? Do you even know what it means? How do you think about prevention instead of reaction?

We know that there are other physicians out there who have bought my book or work through our courses, and they've said, "Look, we're trying to put these principles of Medicine 3.0 into practice ourselves." Our hope is that with each passing day, more and more physicians are taking

the time to reeducate themselves so that indeed they can provide that same level of care.

What do you think about anti-aging drugs like rapamycin, metformin, plasma transfusions and others?

We could say with a very high degree of confidence that rapamycin clearly lengthens the lifespan and improves the healthspan of virtually any animal model it's tested in. Of course, a big question is whether it's going to do that in humans. We're not going to get a direct answer to that question, because the challenge of this field is, how do you test these interventions in humans? How do you test something when your ultimate goal is to understand the impact on length of life over several decades?

When you look at the breadth of information, the understanding of the mechanism of action, the nuance around the varied species that have comparable results in the limited human literature, I would say that rapamycin has crossed a threshold. But it's still not at the point where I would prescribe it to a patient without a lengthy discussion. I am less optimistic on metformin. It doesn't rise to the threshold, though it's a beneficial drug, obviously, for someone who's insulin-resistant or has type 2 diabetes..

What about other drugs?

The class of drugs known as SGLT2 inhibitors probably holds some promise. It's very early days, but it's also possible that we're going to see zero protection, meaning benefits above and beyond the obvious thing that they are doing, out of anti-inflammatory drugs. A very promising study looked at a drug that blocks interleukin 11—it had quite profound results, and I would love to see that replicated and expanded upon. It would make sense that transient blunting of the immune response could be very beneficial to aging.

> "Rapamycin clearly lengthens the lifespan and improves the healthspan of virtually any animal model it's tested in. A big question is whether it's going to do that in humans."

But frankly, for most of the things out there, the evidence is overwhelming that they have zero protective benefits whatsoever. It's a pretty short list of things that are really interesting.

How do you decide what is snake oil and what is real?

At Early Medical, we work really hard at this. We've got an enormous team that works on all of this stuff. You have to look at the sum total of the data. If you're talking about a specific intervention, like a supplement or a drug, you have to look at: How robust are the animal data? How robust are the human data? What is the data for safety? What is the data for efficacy? What is the mechanism of action? You have to go through a very rigorous approach, because the truth is, most things that are proposed as either zero protective or just vaguely, in a hand-waving sense, good for you turn out to be total and utter nonsense at that and, in some cases, actually harmful.

What should the average person do?

Everything that you and I just spent the last few minutes talking about—whether it be supplements or drugs—is rearranging the deck chairs on the *Titanic*. People shouldn't be thinking about any of this nonsense. You have to earn the right to waste time thinking about that stuff, and the way you earn the right is to [first] do the basic blocking and tackling—which, honestly, people don't want to do because it's hard and it takes time.

If people actually want to live longer and better, they need to exercise in a very specific and dedicated manner. They need to stay in energy balance. They need to maintain glycemic control. They need to pay very close attention to how they sleep and manage stress. That is 80 percent of it right there.

You exercise a lot more than what most doctors usually recommend. You walk up hills with weights in a backpack. You spend hours every day training. What about people who can only train, say, half an hour a day?

I promise you that if you were to spend half an hour a day really focusing on how you exercise, you would get far more benefit than you would get by taking a drug like metformin right now.

[**INFOGRAPHIC**]

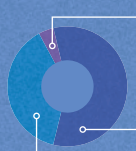
Sleeping Well Can Lengthen Healthspan

High quality sleep is ubiquitous on lists of healthy habits, but just how big an effect does it actually have? In 2021, a team of researchers published the results of a study investigating that question. Using data from the U.K. Biobank, they categorized 328,850 participants according to how well they slept. (The five indicators of poor sleep they used are paraphrased below.) The researchers then tracked participants for about seven years, noting the occurrence of cancer, stroke, dementia, and other diseases and conditions. The best sleepers were 15 percent less likely than poor sleepers to experience a healthspan-terminating event. **By Katie Peek**

Five indicators of good sleep

	Trait prevalance
You generally wake up early.	63%
You typically sleep 7 to 8 hours a night.	69%
It is relatively easy for you to fall and stay asleep.	25%
You do not snore (at least, not loud enough to disturb others).	63%
You stay alert during waking hours, without nodding off.	98%

The number of good sleep indicators a participant exhibited determined their sleep score:

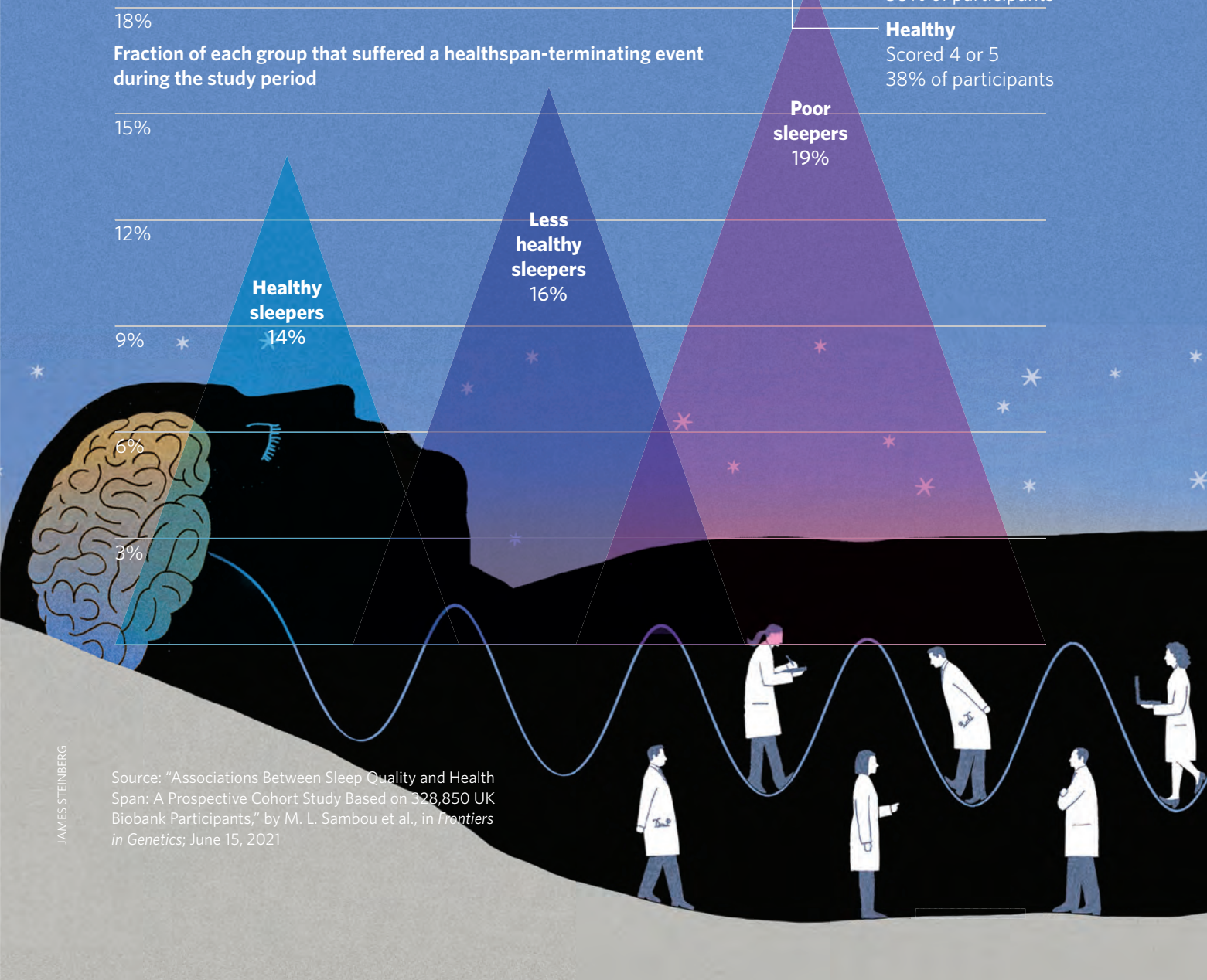


Poor
Scored 0 or 1
4% of participants

Less healthy
Scored 2 or 3
58% of participants

Healthy
Scored 4 or 5
38% of participants

Fraction of each group that suffered a healthspan-terminating event during the study period



Source: "Associations Between Sleep Quality and Health Span: A Prospective Cohort Study Based on 328,850 UK Biobank Participants," by M. L. Sambou et al., in *Frontiers in Genetics*; June 15, 2021

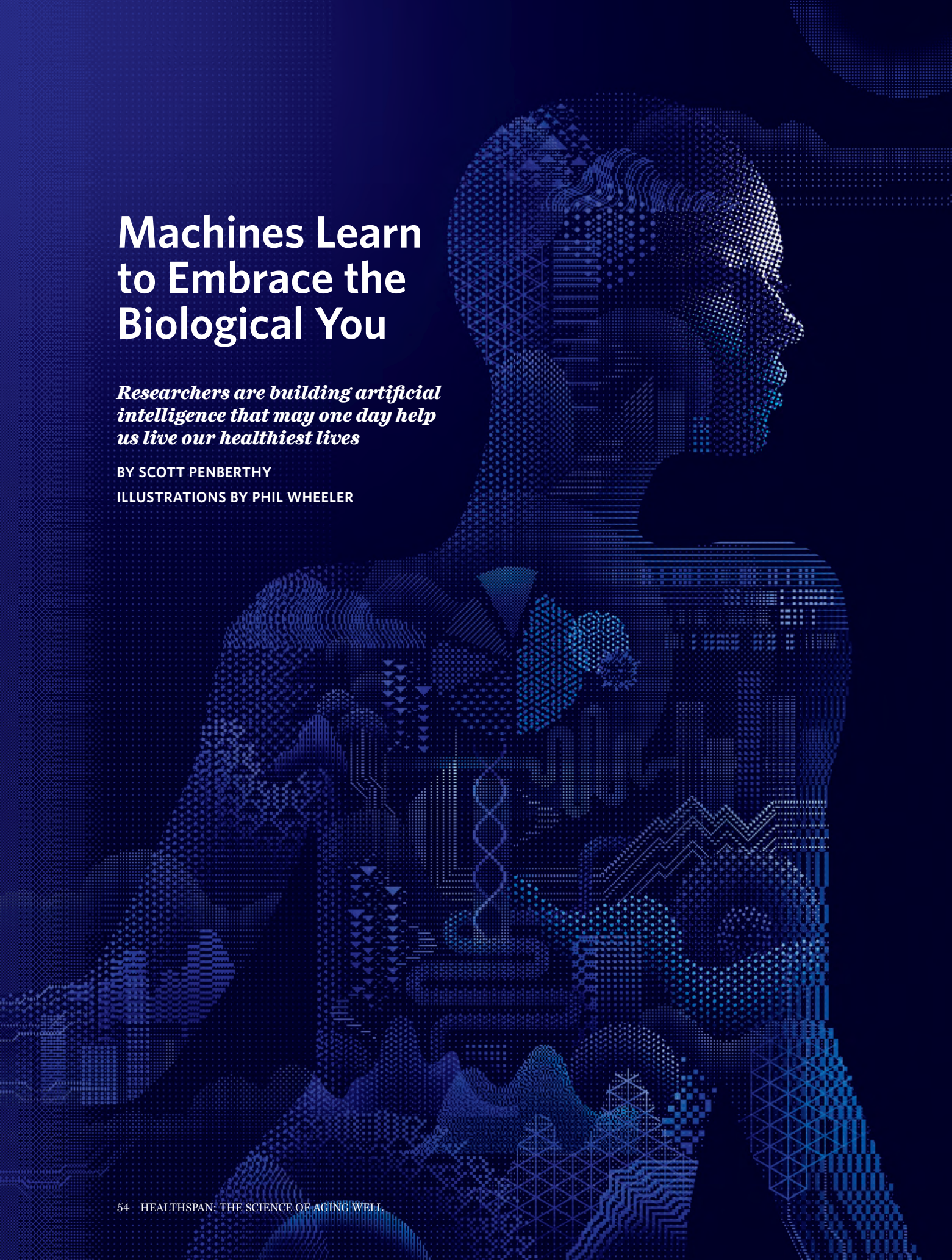
JAMES STEINBERG

Machines Learn to Embrace the Biological You

Researchers are building artificial intelligence that may one day help us live our healthiest lives

BY SCOTT PENBERTHY

ILLUSTRATIONS BY PHIL WHEELER



Imagine your life as a vast landscape, with many pathways representing the myriad possibilities for your future health and well-being. Each choice you make, each genetic trait you've inherited, and every environmental factor you encounter guides you along this landscape's infinite intersecting paths. Some lead toward vitality and longevity, others veer off into illness and decline.

What if you could map such a landscape for your own life, understand its contours, and use that knowledge to steer yourself toward the healthiest possible future?

This vision describes the frontier of artificial intelligence and human health, where data becomes insight, and insight becomes action. By converting vast amounts of diverse data into extremely complex possibilities—or, in the language of computer science, high-dimensional vector spaces—AI is helping scientists visualize this landscape of life and potentially help each one of us steer ourselves toward health and longevity. Being a coder, I prefer to think of this landscape as a manifold—"a collection of points forming … a topologically closed surface or an analog of this in three or more dimensions," as Oxford defines it. The analogy of a manifold captures the complex, multidimensional aspect of AI.

What does navigating the manifold of life mean for you and me? It suggests a shift from reactive to proactive healthcare—instead of waiting for diseases to manifest, we anticipate and prevent them. AI can detect subtle deviations from our optimal path and suggest interventions—lifestyle changes, medical treatments, or environmental adjustments—to guide us back to health.

Imagine receiving personalized health recommendations based on a comprehensive analysis of your genetic makeup, daily habits, and environmental exposures. Wearable devices and health apps could continuously monitor your well-being, providing real-time feedback. These insights could help you avoid chronic illnesses, optimize well-being, and perhaps extend your healthy years well beyond current expectations.

AI is no longer just a tool for crunching numbers or predicting stock markets; it's becoming a compass that can guide us through the complex terrain of our biological existence.

The symphony of data

Think of your body as an orchestra, with each cell, gene, and biomolecule playing its own instrument. Traditional medicine often listens to these instruments in isolation—a gene here, a symptom there.

The true music of health emerges only when we consider the harmony between all these elements. Recent advances make it possible to integrate data from our genomes, microbiomes, lifestyles, and even real-time health metrics like heart rate and activity levels. AI allows us to listen to the entire symphony.

This integration is made possible through a mathematical tool known as embeddings—a mathematical way of representing real-world objects in a way that machine-learning algorithms can digest them. In this sense, a real-world object can be words,

Imagine receiving personalized health recommendations based on a comprehensive analysis of your genetic makeup, daily habits and environmental exposures.

images, audio and so forth. In the case of healthcare, real-world objects can be genomic sequences, MRI scans and other biological data.

Each real-world object is assigned a series of numbers, collectively called a vector. Each number in the vector corresponds to a dimension that defines some characteristic of the object. Together, the values of each dimension represent a point in very high-dimensional space. That point is a computer representation of an idea that captures the relevant information inherent in the original data.

The virtue of defining an object as a vector is that the math we know and use today—dots, lines and curves in two and three dimensions—generalizes well to higher dimensions. The smaller AI models now reason in 768 dimensions; larger ones use 11,000 dimensions or more. Using classic statistics, machines can now find relationships between these points and shapes.

We can then represent a healthy life as a larger mathematical structure made up of many vectors, called a point cloud, which represents our biology and health as we progress through life. This point cloud exists within the larger manifold, which, as indicated earlier, represents all possible health outcomes. As an individual moves through life from one day to the next, the point cloud represents life changes.

It can stay in the region of health, or drift towards that part of the manifold that represents disease.

With these models, based on math and data, we are learning what simple actions we can take to reverse the process of approaching illness and steer our point cloud back to the healthy regions of the manifold.

Clarity from complexity

Transforming the complexity of human health into something that an algorithm can handle would not be possible without some powerful mathematical tools. Variational autoencoders (VAEs) play an important role by compressing intricate data about real-world objects, such as genomic sequences or MRI scans, into simpler representations that preserve essential patterns while discarding unnecessary details. Without VAEs, making sense of the myriad objects in an individual's point cloud would be like trying to take in a complex mural by examining each brushstroke individually. VAEs allow us to step back and see the entire painting.

VAEs do this by taking high-dimensional vectors, which represent the full datasets describing real-world objects, and encoding them into lower-dimensional vectors that still retain the core features most relevant for analysis—a process akin to compressing a high-resolution photograph to a thumbnail. By applying math to these vectors, machines can discover relationships and draw inferences. To borrow an example from large language models, such as ChatGPT or Gemini, it means we can do math on words, such that: king – male + female = queen.

VAEs also introduce mathematical constraints that accommodate computational models called large neural networks. To continue with the example of large language models, these neural networks can be expanded so that the input is not just a word, but a sequence of words.

> Think of your body as an orchestra, with each cell, gene and biomolecule playing its own instrument.

Scientists have expanded on these ideas and generalized the technique to proteins, DNA, sound, images and more. VAEs are now used in analyzing

Catching Cancer

Artificial intelligence trained on millions of pathology slides may improve the ability to diagnose cancer early on

BY DAVID H. FREEDMAN

When trying figure out if a patient has cancer, pathologists still do what they've done since the early 20th century: peer into microscopes at tissue samples from a biopsy or surgical procedure and try to identify the presence of cancer cells. "The process hasn't changed much in 100 years," says Andy Beck, a pathologist and CEO of PathAI.

Pathology is a field that seems ripe for assistance from recent advances in artificial intelligence. Beck's company is one of several that are developing AI models to make the process of diagnosis more efficient and accurate.

PathAI trained its AI models on digitized images of more than five million pathology slides containing 15 million annotations. It also supplemented those images with data on genomes and molecular biomarkers that pathologists don't typically consider, with the goal of generating insight into how particular patients might respond to different treatment options. The models were also trained to identify the tumor's microenvironment, including changes in the blood vessels and noncancerous cells surrounding the tumor, because these changes can provide additional insights into the tumor's aggressiveness and its vulnerability to different treatments.

> "Pathologists can disagree over what the same slide is showing. The algorithms can provide more granularity and reproducibility."

The new AI tools aren't designed to replace pathologists, but to guide doctors toward faster, more accurate and detailed diagnoses by highlighting salient elements in the sample, counting cell types, and quantifying various other abnormal features. The results, says Beck, can in some cases disambiguate tricky diagnostic calls. Getting an early, definitive diagnosis of some

genomic data to predict disease risk. In such healthcare applications, the latent space becomes a common language for different types of biological data, enabling AI to find correlations across diverse datasets. For example, a VAE can help us understand how a specific genetic variant might influence brain structure, linking genomic data with imaging studies in a way that was previously unattainable.

VAEs are also used in analyzing genomic data to predict disease risk. By embedding genetic information into a vector space, AI models can identify patterns associated with conditions like heart disease or diabetes. This allows for earlier interventions and personalized treatment plans, moving us closer to the ideal of precision medicine.

VAEs are not without challenges. Compressing data risks losing subtle details that could be clinically significant. Researchers are working on enhancing VAEs to preserve crucial information while still benefiting from the reduction in dimensions. Advances like hierarchical VAEs, which combine vectors at multiple scales (for instance, using vectors for words, sentences, and paragraphs), aim to retain more nuanced features, improving the utility of these models in healthcare.

Sculpting insights from noise

While VAEs provide a point cloud of embeddings for the computational models, diffusion models are like skilled artists who bring that point cloud to life.

In physics, a diffusion model explains how particles, like molecules in a gas or liquid, spread out over time from an area of high concentration to an area of low concentration by moving randomly, bumping into each other, and slowly moving away from one another. Likewise, a diffusion model in AI starts with a point cloud filled with random numbers, like white noise from an old TV. The diffusion models iteratively refine that image, taking away just a bit of noise at a time, while the embeddings guide the diffusion process to produce what we want.

Diffusion models are trained on pairs of text descriptions and images. They learn how to map from input embeddings, produced by the VAEs, to noise reduction, such that anywhere from 50 to 1,000 steps will produce a pixel-perfect output. I like to imagine a diffusion model as Michelangelo, starting with a block of marble (the noisy data) and chiseling away to reveal a statue (the meaningful insight). Our text embeddings guide the sculpture, "a standing, athletic man named David."

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diseases can be tricky, even for specialists. New AI tools are lending a hand, helping doctors more quickly arrive at clearer, more detailed diagnoses of cancer, inflammatory disease and other illnesses. "There can be disagreements among pathologists over what the same slide is showing," he says. "The algorithms can provide much more granularity and reproducibility."

By improving diagnostics, AI tools will hopefully make it possible for doctors to catch diseases in their earliest stages, when they're more likely to respond to interventions. Catching cancer at the early stages would provide a boost to average healthspan because risks go up dramatically with age—90 percent of cancer cases are diagnosed in people older than 50, according to data from the American Cancer Society.

It's not just the difficulty of tissue diagnosis that opens the door to improvements from AI. It's also a shortage of pathologists—the 15,000 working in the U.S. are far fewer than needed to ensure fast, thorough turnaround of all the tissue biopsies being produced. At the same time, demand is expanding as the population's average age increases, people live longer, and more and better cancer screening turns up more cases.

Exacerbating the problem is the fact that a full cancer diagnosis now calls for greater scrutiny of samples, as slight differences in tumor cells of a given type of cancer can impact the choice of treatment. "As more therapeutic options become available, pathologists need to be as predictive as possible to give patients personalized treatments," says Beck.

As we saw with VAEs, the technique generalizes from text and images. In healthcare, diffusion models can reconstruct high-resolution images from imperfect data, enhance medical imaging, or predict the folding patterns of proteins (a critical factor in drug development). They have been used to improve the quality of MRI scans, allowing for earlier and more accurate diagnosis of tumors or neurodegenerative diseases.

They've also enhanced low-dose CT scans, in which the reduction of radiation exposure usually leads to lower image quality. Diffusion models can take these grainy images and refine them, producing clear visuals that help radiologists detect abnormalities without subjecting patients to higher radiation levels.

By gradually removing noise and focusing on the underlying structures, these models help us visualize complex biological processes with unprecedented clarity. This capability is transforming fields like radiology and pathology, where image quality and detail are paramount.

Control nets: guiding AI with precision

Even the most sophisticated models need guidance to ensure they produce meaningful and accurate results. Sometimes, text isn't enough. It's far easier to show a model where you want something, or place constraints (for instance, "two atoms cannot occupy the same space"), than to describe the outcome.

This is where control nets come into play. These mathematical tools act like a blueprint or wireframe, steering AI models to adhere to specific constraints or desired outcomes. If VAEs and diffusion models are explorers, control nets are the compass, ensuring they stay on course.

For example, in generating a model of a protein, a control net can impose physical and chemical constraints that reflect real-world biological rules. This ensures that the AI produces not only a plausible structure but also one that is biologically feasible and useful for practical applications like drug design.

In the realm of medical imaging, control nets can guide AI to focus on areas of interest, such as highlighting potential tumor regions in an MRI scan. By integrating expert knowledge into the AI's processing, control nets enhance the accuracy and reliability of the results, providing clinicians with actionable insights.

By integrating text descriptions or sample images, control nets guide the AI to generate outputs that align with specific criteria. This precision is crucial when developing treatments or diagnostic tools, where even minor inaccuracies can have significant consequences.

Orchestrating the ensemble

Integrating these powerful tools requires a well-coordinated approach, much like conducting an orchestra. Workflows serve as the conductor, orchestrating the sequence in which VAEs, diffusion models, and control nets operate. They ensure that data flows seamlessly from one stage to the next, maintaining accuracy and efficiency throughout the process.

> We can represent a healthy life as a mathematical structure made up of many vectors, called a point cloud, which represents our biology and health as we progress through life.

Workflows have been common in medicine for decades. They are well documented, tested, multistep plans to produce medicines, run lab equipment, perform surgery, practice medicine and more.

In practical terms, workflows enable us to encode diverse data into a unified format using VAEs; analyze and interpret this data within the manifold of life; diagnose potential issues and predict outcomes; and generate actionable insights or interventions, guided by control nets to ensure feasibility. In drug discovery, for instance, a workflow might begin by encoding molecular structures into vector spaces using VAEs. Diffusion models then explore potential modifications to these molecules, generating new compounds. Control nets ensure these compounds adhere to chemical and biological constraints. Finally, the workflow evaluates the effectiveness and safety of these compounds with robotic labs, accelerating the development of new medications. By automating and structuring these steps, workflows make complex AI processes accessible and applicable in real-world healthcare settings.

Real-world applications

These concepts might sound abstract, but they're already making tangible impacts. Many new companies have begun to apply them to real-world problems.

For instance, Ginkgo Bioworks, a startup, is pioneering the use of AI in synthetic biology. By using

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Dr. Bot Will See You Now

A virtual dermatology clinic uses AI to increase access to timely care

BY ESTHER LANDHUIS

In a 2017 study, researchers showed that AI models could identify skin cancer from images as well as board-certified dermatologists.

At age 22, Susan Conover developed a mole that looked worrying and decided to have it checked out. Her primary care doctor told her he'd typically send her to a dermatologist, in a process that would have delayed its removal and biopsy by three months, she recalls. "But we don't have time to waste," he told her.

Instead, her primary care doctor did a biopsy. The results: melanoma. "If I had waited to go to a dermatologist," she says, "I might not be here."

Conover's story had a happy ending—the cancer hadn't spread. But not everyone is so lucky. Skin disease affects one in four people in the U.S., and trained specialists are in short supply. A 2018 survey found that in Boston, which boasts state-of-the-art hospitals, patients waited an average of 52 days for an initial consultation and four to nine months to see a specialist.

Her terrifying experience galvanized Conover to do something about the situation. In 2017, she founded a company, Piction Health, to build a mobile app to help primary care physicians recognize melanoma from images.

Then came the pandemic and the rise of telehealth. More than 96 percent of dermatologists offered their services via telehealth during the pandemic. At the same time, artificial-intelligence models were getting better at diagnosing moles and rashes from images. In a 2017 study, researchers showed that AI models could identify skin cancer from images as well as board-certified dermatologists. In a 2020 study, led by a team at Google Health, AI performed on par with specialists and better than general practitioners and nurses in recognizing conditions commonly seen in primary care.

Piction changed course in part to capitalize on these trends. It developed an AI model and trained it on 750,000 images from more than 200 dermatologists across 20 countries—including Bolivia, South Africa, India, Tunisia and some from Europe—to ensure a representative mix of skin tones. In preliminary analyses of the same 26 common skin conditions used in the Google Health study, "our AI models generate the top-5 conditions list with the same accuracy level as a dermatologist," says Pranav Kuber, a co-founder and chief technology officer. The company claims its AI model makes accurate identification and treatment faster and easier for doctors. Its early data, which has yet to be published, suggests that it can reduce their evaluation time from 15 minutes to three.

In December 2022, Piction opened its own online-first clinic. Patients submit photos to Piction dermatologists, who use the firm's AI model to produce a short list of potential diagnoses and identify patients who, like the young Conover, should be fast-tracked for in-person examination in partner clinics, where specialists make the diagnoses and fashion a treatment plan. The goal, says Kuber, is that patients can be seen "within a two- to three-week period instead of waiting months."

As of October, 3,000 patients had used Piction's clinic. So far, it is available in Connecticut, Florida, Massachusetts, New Hampshire and Washington. The service is covered by several major insurance companies, or patients can pay $119 out-of-pocket for each consultation.

Eleni Linos, a professor of dermatology and epidemiology who directs the Stanford Center for Digital Health, and who has no connection with Piction, says: "I'm really optimistic about how this technology can help patients get the best care they can get, while at the same time helping doctors."

Esther Landhuis is a freelance journalist in the San Francisco Bay Area.

VAEs to embed extensive protein and genetic data into vector spaces, they can design novel organisms and biological processes. This approach is streamlining the creation of custom enzymes and microorganisms for pharmaceuticals, agriculture, and even environmental remediation. And Every Cure, a nonprofit organization, is leveraging AI to uncover new applications for existing drugs. By mapping drugs within a high-dimensional manifold of biological effects, their AI systems can identify potential treatments for diseases lacking effective therapies. This approach not only reduces development time but also cuts costs, making treatments more accessible.

Hospitals are adopting AI workflows to improve diagnostic imaging. For example, Siemens Healthineers uses AI to enhance MRI and CT scans, improving image quality and reducing scan times. Diffusion models and control nets work together to produce clearer images, aiding in the early detection of diseases like cancer and improving patient outcomes.

Researchers at MIT and McMaster University have used AI models to sift through millions of chemical compounds, identifying new antibiotics capable of combating drug-resistant bacteria. By integrating VAEs and diffusion models, they rapidly discovered a molecule named halicin, which has shown effectiveness in the lab against a range of pathogens, including those resistant to existing antibiotics. Versions of halicin are now in clinical trials.

Google DeepMind's AlphaFold project has transformed our ability to predict protein structures. By employing advanced AI techniques, AlphaFold can determine, with remarkable accuracy, the three-dimensional shape of proteins based on their amino acid sequences. This breakthrough is accelerating research in areas ranging from drug development to genetic diseases. Google has created a company, Isomorphic Labs, to pursue commercial applications.

Ethical considerations and future outlook

As we embrace these advanced technologies, at least three ethical challenges need attention. First, handling sensitive health data requires stringent security measures to protect patient confidentiality. In this

AI for What Ails You

Powerful new models promise to accelerate the process of drug discovery

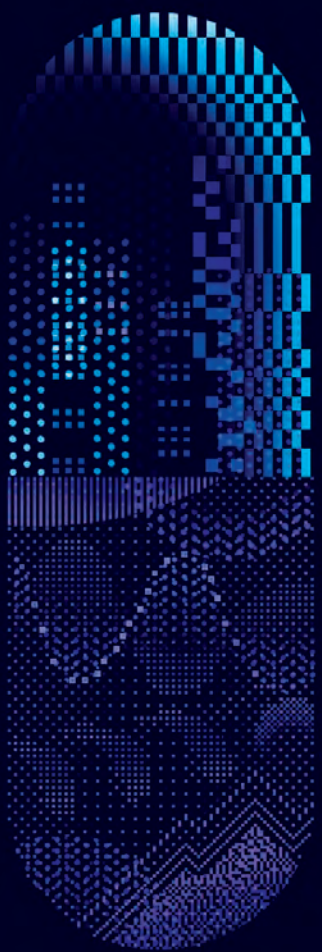
BY MIKE MAY

The news in October 2024 that Sir Demis Hassabis would receive a Nobel in chemistry for his work on predicting protein structures put the recent rise of artificial intelligence for drug discovery in the spotlight.

Powerful new AI models can comb through datasets to identify promising molecules and predict their interactions with biological targets. Other models can predict how safe and effective an experimental drug is likely to be. Together, these models are showing great potential in accelerating the process of drug development.

Efforts to apply AI to drug discovery have had to overcome a particular challenge: a paucity of data upon which to train models. There is usually only a limited amount of data on a potential drug and how it might affect a disease. "Many drug targets are novel, and they have very little or no known chemical matter that modulates them," says Evan Feinberg, founder and CEO of Genesis Therapeutics.

To cope with the paucity of data, scientists are having to dig deep into their programming toolkit. A machine-learning model for drug discovery might start with data based on what's known about the molecular structure of a disease-related receptor and then generate theoretical molecules until some are found that would bind to that receptor. To develop such AI-based methods to search for new drugs,



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The integration of AI into healthcare promises a future in which personalized medicine is the norm.

regard, ensuring compliance with regulations like HIPAA and GDPR is essential. Second, it is also essential to make the benefits of AI-driven healthcare accessible to all, regardless of socioeconomic status or geographic location. Bridging this digital divide is necessary to prevent widening health disparities. Third, AI models can be complex and opaque. Developing methods to interpret and explain AI decisions builds trust among clinicians and patients, paving the way for adoption.

As we look ahead, the integration of AI into healthcare promises a future in which personalized medicine is the norm. Continuous learning from new data will make AI systems more accurate and adaptable. The potential to predict and prevent diseases before they manifest could transform healthcare from a reactive to a proactive paradigm.

As these technologies continue to evolve, they hold the promise of demystifying diseases, personalizing treatments, and ultimately enhancing the human experience. The journey through the manifold of life is one of discovery, not just of the world around us but of ourselves. And in this journey, AI doesn't replace the human element—doctors and other healthcare providers—it enriches it, providing us with deeper insights and empowering us to make informed choices about our health and well-being.

Through AI, we're not just collecting data; we're gaining insight into the very fabric of life. Carl Sagan, the astrophysicist and science communicator, once said: "We are a way for the cosmos to know itself." We are now learning to read the complex code that shapes our existence, and with that knowledge comes the power to shape our future.

Scott Penberthy, Ph.D., is chief technology officer of healthcare and life sciences at Google.

"We will find the best new drugs by pairing the smartest scientists with the most powerful AI platform."

though, companies must build custom algorithms and models. Genesis, for instance, approaches drug discovery with a combination of proprietary AI-based models and laboratory studies of molecules.

Hassabis, who is CEO at Google DeepMind and Isomorphic Labs, both owned by Google's parent company, Alphabet, was instrumental in developing AlphaFold, one of the highest-profile AI platforms. The latest version, AlphaFold 3, predicts the 3D structure of proteins and how they interact with other biomolecules, such as receptors and enzymes, in the progress of disease. Scientists at Isomorphic are collaborating with teams at Eli Lilly and Novartis to combine AlphaFold 3 with other custom AI-based tools to discover antibodies and other new treatments that inhibit disease-related targets.

What is reportedly the first AI-designed drug, to treat a rare lung disease, started phase 2 clinical trials in June 2023. Biotech firm Insilico Medicine developed it using its PHARMA.AI software suite. This AI-driven approach analyzes disease targets based on many features, including how likely they are to be safely and effectively inhibited by potential drugs. "This holistic evaluation is crucial for the identification of viable therapeutic targets," says Thomas Leichner, the firm's head of strategy.

Genesis's AI software for drug discovery—its GEMS platform (for Genesis Exploration of Molecular Space)—uses large language models to create billions of druglike molecules. Then, it uses machine-learning algorithms to predict a protein's potency and selectivity for a specific disease target. In 2024, pharmaceutical company Gilead Sciences began using GEMS in collaboration with Genesis.

Although most academic scientists don't have access to the new tools, more companies offer cloud-based services. For instance, Ginkgo Bioworks, which develops methods of programming cells to make drugs and other products, now offers its AI models via Google Cloud.

As the Ginkgo-Google collaboration suggests, AI models are only a tool in the process of drug discovery. "We will find the best new drugs by pairing the smartest scientists with the most powerful AI platform," says Feinberg. "And I think that synergy will continue for some time."

Mike May is a freelance writer.

The Longevity Economy

A five-year-old today has an extremely good chance of living to 90 and beyond. To cope, we need an economic and cultural revolution aimed at changing how we age

BY ANDREW J. SCOTT

ILLUSTRATIONS BY DARIA KIRPACH

Extending life expectancy was one of the outstanding achievements of the 20th century. A baby born in 1900, when infectious disease outbreaks were a regular occurrence and chronic diseases like cancer, dementia and heart disease were barely understood, lived just 32 years, on average. A baby born in 2021, after more than a century of modern medical research, will live to an average of 71.

At the same time, fertility rates have plummeted worldwide. In 1950, the average woman gave birth to nearly five children. Today that number is just over two—barely enough to maintain a stable population.

Fewer parents mourn the loss of their infants, fewer children have parents snatched away in midlife, and more grandparents get to meet their grandchildren. But despite this stunning progress, few people are jumping up and down with excitement. The usual response is pessimism and worry.

At the heart of this reaction is a shift. In the 20th century, improvements in public health and advances in modern medicine reduced infant and midlife mortality and boosted life expectancy. These extra years of life were gained when people were mainly in good health and at their most productive. Now, most life-expectancy gains in high-income countries arise from declining mortality rates after 70 years of age, and a growing chance of living into your 90s. And for more and more people, the extra years of life coincide with declining health and economic inactivity.

Policymakers worry that this shift will lead to a dwindling workforce that's unable to support the needs of an ever-expanding older population, including their needs for income, healthcare and living assistance. The fear is that pension deficits will become unsustainable, health expenditures will rise and economic growth will decline. By 2050 gross domestic product (GDP) per capita will drop by an average of eight percent for the nations of the Organization for Economic Cooperation and Development (OECD), the group predicts, plummeting 15 percent in South Korea and Italy and more than 20 percent in Spain.

When only a minority can expect to live to old age, it isn't worth it, economically speaking, for society to invest in ensuring they live long, healthy, and productive lives into their 80s. When it is the majority, it becomes an imperative.

If we are to avoid the worst predictions of an aging society, we need to focus on creating a longevity society that supports the length of life we can now expect. We need radical adjustment and adaptation to ensure life isn't only longer, but also healthier, productive and engaging for longer. With global life expectancy exceeding 70, and half of children born today in high-income countries expected to live into their 90s, the first longevity revolution has ended—the young can now expect to become the old. A second longevity revolution must now begin, aimed at changing how we age.

A historic miscalculation

In 1798, the renowned economist and demographer Thomas Malthus argued that "the power of population is so superior to the power of the Earth to produce subsistence ... that premature death must in some shape or other visit the human race." Malthus feared that society would be unable to provide the resources that extra mouths require and that overpopulation would inevitably result in famine, disease and war. Similarly, many in our aging society fear that we will be unable to provide the resources that the extra years of longevity demand.

> Medical progress has achieved wonders at keeping us alive for longer but not in keeping us healthier. We have hit diminishing returns. We need a new approach.

Malthus's insights have been hugely influential and continue to resonate as the world wrestles with the implications of climate change. But Malthus wrote at a time when the global population was approaching one billion; today it exceeds eight billion.

Central to Malthus's near-term miscalculation was his failure to foresee the impact of the then-nascent Industrial Revolution. A powerful mix of ingenuity, innovation, investment and institutional change led to increases in productivity that helped provide additional resources to support a larger population. As a result, resources increased to levels that helped boost investment in health and education, leading to further gains in productivity, life expectancy and population.

To create a second longevity revolution, we need a mix just as powerful. Until now the proportion of lifespan that is healthy has remained approximately the same, even as life expectancy has increased, though the details differ in different countries.

Increases in life expectancy have transformed the global burden of disease so that now the most common causes of death and illness globally are predominantly those whose incidence increases with age—cardiovascular disease, cancer, pulmonary disease, dementia, and so forth (see 'The Conditions That Shorten Our Healthspan' on page 12). The biggest lifetime health burden a newborn child will face is these aging-related diseases.

Medical progress has achieved wonders at keeping us alive longer, but not while keeping us healthier. We have hit diminishing returns. We need a new approach.

Improving how we age

Malthus's pessimism has echoes today in the pessimism around the economic prospect of an aging society. His mistake may echo as well. Whatever the merits of his logic, he dramatically underestimated humanity's ability to support a large population. Might the same be true of an aging society?

When people talk about artificial intelligence and climate change, they often emphasize the need for radical adjustment and adaptation. But talk about the challenges of an aging society rarely goes beyond raising the retirement age, cruise ships, care homes and adult diapers.

Rather than obsessing over all those people who are now older than 65, we need to focus on the future—specifically, what to do about today's five-year-olds, who have extremely good odds of living to 65 years and beyond. Specifically, there's an urgent need to ensure that our healthspan—the number of years we spend in good health—extends to match our new lifespan.

Improving how we age offers the prospect of enormous benefits for health and well-being as well as the economy. Using economic tools to place a dollar value on health gains, my colleagues and I estimate that slowing down the rate at which Americans age enough to boost life expectancy by one year, while also lowering morbidity rates, would yield $37 trillion of current and future welfare. Crucially, the analysis reveals that lowering morbidity to the point where healthy life expectancy is the same as life expectancy is far more valuable than any further increases in life expectancy.

Tackling how we age requires a major shift in how we think about health. The gains in life expectancy over the 20th century came from remarkable progress in tackling various diseases such as typhus, smallpox, cholera, and tuberculosis. Health systems around the world have responded to these breakthroughs by successfully intervening to treat disease and thereby boosting life expectancy.

Today we need to shift our focus to prevention and keeping people healthy. Aging-related diseases are chronic and long-lasting, so it is best to delay their incidence rather than intervene when they occur. Once an individual experiences one chronic disease, the likelihood of experiencing a second increases, leading to multiple-morbidities. All this points to a focus on intervening upstream to prevent the incidence of aging-related diseases.

This is why there is so much excitement about the emerging field of geroscience and its recent advances illuminating the biological pathways of aging. The hope is that better understanding will ultimately lead to treatments and therapeutics that slow down the aging process keep us healthier for longer. The potential gains of focusing on the underlying aging process, rather than tackling myriad individual diseases, are large. Since aging is an underlying risk factor for multiple diseases, success in improving how we age leads to gains across multiple illnesses. The effect of reducing multiple diseases unlocks an important complementarity: the gains from reducing the risk of cancer are greater when you do not run the risk of experiencing dementia, and vice versa.

Rather than obsessing over all those people older than 65, we need to focus on what to do about today's five-year-olds.

The economics of healthy aging

If we manage to keep ourselves healthy for longer, we unlock not only health benefits but economic ones as well. In response to growing life expectancy, governments worldwide are increasing the eligibility age for state pensions. In 1983, the U.S. began increasing the retirement age from 65 to its current 67. According to OECD data, 22-year-olds in Denmark will have to wait until they are 74 before collecting a state pension. However, these measures assume individuals are capable of working for that long; right now, around 80 percent of Americans are working at age 50, but by 65, it has fallen to around a third. If most people have already left the labor market, there would be no point in raising the state pension age—it would cause financial hardship for many people.

DARIA KIRPACH

The reasons for withdrawing from the labor market are varied, but high among them is poor health—either for the individuals themselves or because they need to care for a family member. For instance, in the U.K., someone who is in their 50s is six times more likely to leave the labor force if they have a cardiovascular event than if they don't. With an aging population, that makes preventive health measures ever more valuable.

The need to invest in health for the sake of the economy has become increasingly apparent as populations age. Over the past 10 years, most of the employment growth in high-income countries has come from workers aged over 50, and in the European Union, it's more than 100 percent. As the population ages, so does the labor force, making health and GDP increasingly intertwined.

The gains we've already seen to life expectancy need to be matched with efforts to make life not just longer but healthier, productive and engaging for longer. This is the longevity imperative that societies face if they are to avoid rising healthcare costs, growing pension deficits and stalling economic growth. The required social changes that this longevity imperative demands are broad and profound. As with the transformation that undermined Malthus's pessimistic predictions, we will need widespread ingenuity, innovation, investment and new institutions.

Advancements in geroscience promise to play a key role in helping us age better and reduce morbidity. Given that the richest Americans live more than 10 years longer than the poorest, it's also clear that policies aimed at tackling socioeconomic inequalities are also key. These inequalities show that we already know how to slow down aging for some, and a priority must be ensuring this occurs for many. It would help to prioritize inexpensive treatments that benefit the many, rather than expensive treatments that radically prolong life for a few.

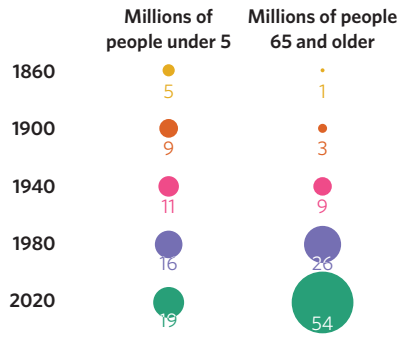
An evergreen economy

Major cultural change will also be required. Ageism involves underestimating the capacity of older people and our own later years. The fact that an "aging society" is seen as a problem speaks volumes about ageism. But in a world where the young can now expect to become old, we need to invest in our own futures and cannot afford to be prevented by ageist attitudes. If we wish to age better, we cannot wait until we are old to start doing so. If we do not invest in our newly found longer lives, then we run the risk of spending them in poor health and with too few resources.

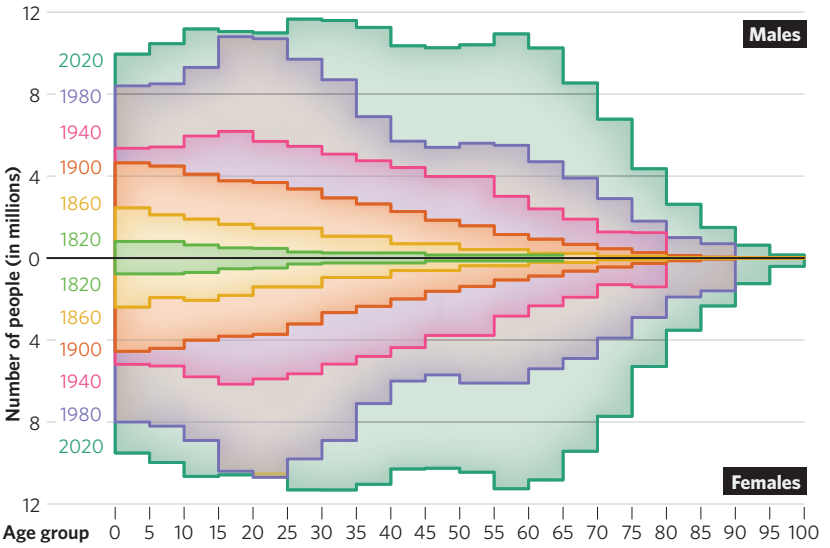
Much else needs to change. While there is much talk of a "silver economy" providing the resources older individuals require, there needs to be the development of an "evergreen economy" focused on supporting aging better. Currently, only around three percent of government health expenditures are on prevention. That needs to increase in a way that encourages innovation in prevention. As the health system shifts from focusing on disease to promoting health, this agenda will spread beyond hospitals and medics to include food and drink, public housing and transport, and much else.

The Shifting Age Distribution of the U.S. Population

Throughout human history, the young have far outnumbered the old. But in wealthy countries, that has shifted in recent decades. The U.S. now has nearly three times as many residents age 65 and older as it does kids under 5. Compare that to 1860, when the youngest age group outnumbered the oldest 5 to 1.



Source: U.S. Census Bureau



If people work longer, they will also need to be skilled for longer, which will generate increased demand for education around lifelong learning and career transitions. The financial sector will also need to respond because longer careers will require a more complex pattern of accumulation and decumulation of financial assets than the current simple pension model. In addition, while the 20th century saw the growth of an enormous life insurance industry aimed at eliminating the financial risk of dying early, in the 21st century, as more people live to 100 and beyond, a new form of insurance will be required to ameliorate the risk of running out of money.

If people work longer, they will also need to be skilled for longer, which will generate increased demand for education around lifelong learning and career transitions.

For the first time, the young can expect to live into their tenth decade or even longer. This makes radical social change inevitable. We are entering a potentially dramatic turning point in the human condition.

When infant mortality was the biggest health challenge, resources were focused on tackling that problem. As progress was made, attention shifted to the diseases of middle age. Now, the majority of people will become old, and increasing attention will be placed on geroscience and understanding aging-related diseases.

There is something different, however, about aging-related diseases, compared to infant or midlife diseases. The better we age, the more valuable further improvements become. When we are ill in our 80s, living into our 90s holds limited appeal. But when we are healthy and productive in our 90s, we become interested in living beyond 100. There are increasing returns to improving how we age that didn't exist for infant or midlife mortality improvements.

None of this implies that geroscience is guaranteed to deliver sporty 120-year-olds. The biological mysteries of aging may remain forever too complex to understand or manipulate. It does point, though, to the need to invest in improving our understanding of how we age. Given the life expectancy we can now expect, few things are as crucial to our individual and collective future. Humanity is entering a radically new era.

***Andrew J. Scott is a professor of economics at London Business School and director of economics at the Ellison Institute of Technology. He previously taught at Oxford and Harvard University and the London School of Economics. He is the author of the recently published* The Longevity Imperative.**

Community and Hard Work

Aziz Gündogdu grew up in a rural village with few material things, but he had the comfort and support of family and community. "There was poverty back then, but people loved each other very much," he said. "They helped each other a lot."

After a stint in the military, Gündogdu worked much of his life as a farmer. He appreciated the value of hard work. He was able to remain active into his 100s, he believed, because he never stopped doing physical labor, and watching what he ate.

At 102, Gündogdu was still tending the garden in his yard and taking long walks around Doğanca, a village in northwestern Turkey.

"The reason I have lived this long," he said, "is because I drink goat's milk."

Sources: Alamy and *The Star Online*

DPA PICTURE ALLIANCE / ALAMY STOCK PHOTO

The Social Side of Healthspan

To take full advantage of the latest science of wellness, the U.S. will have to address many social inequities that jeopardize people's health

BY ROBERT LEE KILPATRICK

ILLUSTRATIONS BY MARK SMITH

Two years ago, during a routine physical, my doctor told me I was developing diabetes. My fasting blood sugar levels were rising and also becoming erratic. After my doctor prescribed a course of medication, I asked him whether losing weight and exercising would bring my blood sugar levels into a normal range. "Probably," my doctor said.

I decided to try intermittent fasting. I didn't think I'd be able to fast 16 hours a day. But I have done it for 515 consecutive days, and I have reduced my blood sugar and weight to sustainably healthy levels.

Many Americans are not so lucky. U.S. health outcomes consistently rank poorly among high-income countries. Among OECD nations, for example, the U.S. has the lowest longevity from birth, along with the highest rates of maternal and infant mortality and death from treatable disease. The U.S. has twice the obesity rate over the OECD average and among the highest suicide rates.

Paradoxically, the U.S. spends nearly twice as much on healthcare as any other high-income country. In other words, the U.S. spends more on healthcare and gets less.

Healthcare experts explain the contradiction in a multitude of ways, but the root cause is largely outside medicine. Some of the most powerful determinants of healthspan—living healthy for longer—are social. Income, education, social connection, job stress and social status all factor into a patient's access to quality care. Inequities implicit in those factors are, in turn, mirrored in healthcare statistics. The result is that good healthcare in the U.S. is simply out of reach for many people.

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I am fortunate enough to be one of the exceptions. I collaborate with two leading healthspan researchers—Leroy Hood at Phenome Health in Seattle and Eric Verdin, CEO of the Buck Institute for Research on Aging—who both recommend intermittent fasting as a way to help extend healthspan. I am also educated, and I have sufficient income and a supportive community.

Social determinants of good health like these must be addressed to improve healthspan for everyone. That's possible. Just as there are communities suffering across the U.S., there are communities that are thriving. Decision-makers have access to the science and the data that reveals what separates the two. What's lacking is a commitment to policies that prioritize population health, and the will to enlist the public and private sectors to build a new society focused on the health of all individuals.

Simple question, difficult answers

The Jesuits have a concept for living: *cura personalis*, or "care for the person." It implies a dedication to promoting human dignity and care for the mind, body and spirit of the whole person. In secular terms, this concept translates to Whole Person Health Care, which, according to the National Center for Complementary and Integrative Health (NCCIH), considers "multiple factors that promote either health or disease" and empowers individuals, families, communities and populations to improve their health. Whole Person Health Care embraces multiple dimensions of wellness, including physical, emotional, spiritual and social.

Understanding how an individual lives can offer clues, drawn from population data, about how that person might age. The first telling question is, Where does that individual live? Data from a county or even a zip code contains a multitude of healthspan information.

The goal is to bring impoverished areas closer to the level of wealthy ones, such as Marin County, California, a suburb of San Francisco. Marin County ranked as the state's healthiest county, as measured by the 2024 County Health Rankings & Roadmaps, a report put out by researchers at the Population Health Institute at the University of Wisconsin–Madison. It scores highly in quality of life, clinical care, and other social and economic factors. According to *U.S. News and World Report*, Marin County ranks fifth among counties nationally in terms of median household income.

The story is far different in Fresno County, which is located in the Central Valley, where the economy is mostly agricultural. The average resident of Fresno County can expect to live eight years less than residents of Marin County. It has twice the burden of premature deaths. Twice as many residents are physically inactive, smoking rates dwarf Marin County and 50 percent more residents are obese. Twenty-seven percent of residents live in poverty, versus eight percent in Marin County.

In Fresno County, zooming in further offers a more complex picture. Researchers at two institutes

at Fresno State University—the Joint Center for Political and Economic Studies and the Central Valley Health Policy Institute—analyzed data from a national repository called PLACES that makes localized health-related data, including chronic disease burden, available to counties across the country. PLACES—a collaboration of the Centers for Disease Control and Prevention, the Robert Wood Johnson Foundation and the CDC Foundation—aims to help local health departments and jurisdictions understand health disparities in their area and better plan public-health interventions.

Similar health disparities by region, county and even neighborhood are common across the U.S. Without data, and without the willingness to use it to guide policy and healthcare recommendations, such problems will remain invisible. Bridging the gap between wealthy and resource-deprived counties will require new policies at the federal, state and community levels geared to building a healthy population. These policies must be data-driven and consider the social determinants of health, chief among them where a person lives and what resources they have access to.

A true safety net

Another factor that contributes to the healthspan gap is how the U.S. supports its elderly. Many are simply not prepared for the financial burden of living longer. Despite the existence of Social Security and Medicare, many are in danger of outliving their savings. About half of those over the age of 65 live in households that rely on Social Security payments for at least 50 percent of their family income; for a quarter of them, Social Security benefits make up at least 90 percent of their family income.

With the future of entitlements uncertain, most Americans will need to become economically active longer. This will involve putting in place workforce initiatives like those of the AARP Foundation, which include Digital Skills Ready@50+, which helps people retrain for new types of work, and the Senior Community Service Employment Program, which helps unemployed people over 55, including low-income people, hunt for work. The reality is that aging is the greatest risk factor for most chronic diseases, and along with aging for most people comes a reduction in income. For many workers in the gig economy, it is not possible to earn enough money to support a healthy life, no matter how hard they work.

In the creation of a support structure, for people of all ages, the role of community must also be considered. Recent research has shown that social health and community have an outsized impact on healthspan. As a result, the World Health Organization (WHO) has issued a call to make social connection a global health priority. U.S. Surgeon General Vivek H. Murthy's report, *Our Epidemic of Loneliness and Isolation,* puts the number of adults experiencing loneliness in the U.S. at one in two. It is associated with a greater risk of cardiovascular disease, dementia, stroke, depression, anxiety and premature death. "Loneliness is far more than just a bad feeling—it harms both individual and societal health," the report says.

> By improving healthspans for individuals we will be able to create a more equitable and just society.

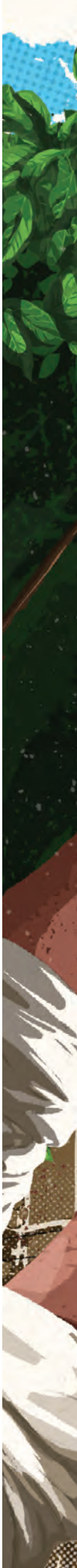
Conditions of housing and the environment also have an impact on healthy aging. This includes larger environmental influences such as air and water quality, safety and access to nutritious and affordable food, but also access to green spaces and cultural opportunities. Initiatives such as community gardens, which are popular in parts of Europe and the U.S., can help people connect to the living world, forge new friendships, and provide a sense of awareness that personal wellness and environmental wellness are intertwined.

Efforts are underway in the U.S. to "regreen" cities. One of the pioneers is the Bezos Earth Fund, whose aim is that "living in a city should not have to mean living without nature. Green spaces such as parks, community gardens, nature trails, and tree canopies along city blocks are vital to the health and well-being of all Americans. And as extreme weather events and record-breaking temperatures become more frequent, urban green spaces play an ever more crucial role in climate resilience for all communities."

A generational goal

Since healthspan is so heavily influenced by social factors, improving it will take a commitment to true social change. That does not come quickly. The U.S. needs a long-term strategy to bring its healthcare provision into alignment with those of other wealthy nations, to succeed where we've failed before.

Based on successful efforts in the U.S. and abroad, we now know how. The solutions include changing the healthcare focus from treating chronic disease




MARK SMITH

to preventing it. Leroy Hood's vision of P4 Medicine offers a promising path; it uses data and science to predict a person's future health and steer them to implement measures that prevent chronic disease.

We need a system that is organized and paid for by a single payer, and it needs to offer healthcare to everyone, regardless of ability to pay. A non-profit foundation could be both the payer and provider, something Kaiser Permanente (KP) already does in California. Governments can as well, as they do in many other developed countries, including U.K., Canada and Japan. In the U.S., state-level legislation is being piloted, based on this thinking. For example, a California law that went into effect in 2023 would create a waiver to federal law that would allocate Medicare and Medicaid funds to a state-level single-payer system financed by state and federal funds.

Public education is essential. Examples include the Live Longer Better campaign in the U.K., led by Sir Muir Gray of Oxford, which aims to reduce risk and extend people's healthspans in measurable ways by increasing their physical, cognitive and emotional activity. Shifting the food system is also essential. It should be based on nutritional science and supported by policies like that proposed by Robert H. Lustig, a San Francisco–based physician and chief science officer of Eat Real, a nonprofit that aims to provide nutritious and subsidized meals in U.S. schools. Affordable housing is a must, along with initiatives like Finland's Housing First plan, which has almost completely eliminated homelessness in the country by creating group homes that provide unhoused people with small apartments, addiction treatment, and other care. Without a home or shelter it is close to impossible to live a long and healthy life.

As the above examples suggest, science is only half the answer. This challenge is as much moral, political and economic as it is scientific.

It is fair to ask, "Who is increased healthspan for?" The best answer is, for all people. By improving healthspans for all individuals we will be able to create a more equitable and just society.

Robert Lee Kilpatrick is Co-founder of the Radical Health Foundation and was recently an academic visitor at the University of Oxford. He is an adviser to Berkeley SkyDeck, an adviser to the Columbia University Master of Science Program in Bioethics, chair of the Health & Medicine Member-Led Forum at the Commonwealth Club World Affairs, and a partner at the Technology Vision Group. He received a doctorate in the history of medicine from the University of Cambridge.

Healthy Smile

Oral healthcare is shaping up to be a key component of the effort to increase healthspans

BY LISA SIMON | ILLUSTRATION BY MATTIA RIAMI

For much of human history, aging meant losing teeth. Many historical portraits feature subjects, stoic and unsmiling, doing their best to hide decaying teeth. Thanks to advances in dentistry and public health, those days are largely over. For Americans, edentulism, or the complete loss of teeth, is no longer considered inevitable, and most today can expect to keep their teeth for a lifetime.

Despite those developments, significant room for improvement remains. The Centers for Disease Control and Prevention found that between 2009 and 2014, about 40 percent of American adults 30 years or older, and 60 percent of Americans over 65, had some form of periodontitis, a severe inflammation of the gums resulting from tooth decay.

A systematic review found 15 studies demonstrating that daily toothbrushing decreases death among patients admitted to the intensive care unit.

The issue extends far beyond oral hygiene. As dentists and researchers uncover the links between oral health and chronic disease, they're finding that the healthier the teeth and gums, the healthier the body. For longer, better lives, the state of our teeth and gums deserves a closer look.

Gateway to health

At its root, periodontal disease is an inflammatory condition. The invasion of anaerobic bacteria at the junction of tooth and bone unleashes a cascade of immune responses. When oral bacteria enter the system, through either an airway or a wound, they can fuel further inflammation.

Research in recent decades has demonstrated links between poor oral health and diabetes, heart disease, autoimmune disorders, and even dementia—all of which are suspected to be inflammatory diseases. This makes sense. The surface area of oral tissue is roughly equivalent in size to the palm of a hand. Inflammation over such an area has been shown to worsen the effects of high sugar in diabetes and damage the endothelium of arteries in vascular disease. Periodontal treatment is known to reduce levels of inflammatory markers in the blood, such as C-reactive protein.

Inflammation is not the only way that oral health impacts health. A systematic review found 15 studies that demonstrated that daily toothbrushing decreases the incidence of death among patients admitted to the intensive care unit, most likely by preventing bacteria from the mouth from traveling into the lungs. Older adults without teeth are more likely to have depression and report social isolation, because having teeth allows us to speak well and participate more fully in community. Studies have found lower levels of iron and vitamins A and C in the blood of older adults with dentures, because these nutrients are typically found in nutrient-dense foods like meat and vegetables, both of which can be difficult to chew.

Teeth even play a role in financial security and success. A study by economists Sherri Glied and Matthew Neidell found that women from low-income families who grew up in counties with water fluoridation earned wages that were 4 percent higher than those without fluoride access. The authors excluded factors such as these groups choosing different jobs or being more or less productive than each other. They concluded the wage difference was largely because the subjects' healthier smiles meant that employers (and, presumably, tipping customers) preferred them.

Golden age of dentistry

In the past two decades, dentistry has made remarkable technological advances. Tooth-colored composite materials can make fillings nearly invisible; they survive longer in the mouth with less risk of new decay and require the removal of less healthy tooth structure than older materials. Crowns can be color-matched using artificial intelligence and fit with a custom scan. The first human trial of a drug to regrow a lost tooth began last September. Scientists are developing a caries vaccine that could target *Streptococcus mutans*, the bacteria most responsible for dental decay.

Patients can now receive a crown produced from 3D mouth scans within the same day as their visit. Instead of having to be anesthetized in an operating room, very young children can have their cavities arrested completely with a thin coat of silver diamine fluoride, which could soon be used in nursing homes, rehab facilities and even doctors' offices.

Dental implants have revolutionized tooth replacement by providing a natural-looking tooth that is fully integrated with the jawbone. For people missing all their teeth, dentures attached to just two implants in the lower jaw can dramatically improve the ability to chew while also making the denture look more natural. In the future, lab-grown teeth may offer a biological replacement that could fully restore a smile.

The question today is, How can we ensure that good dental care reaches everyone?

A mandate for health

Dental problems used to be more prevalent among the wealthy than the poor, mainly because the rich had greater access to sugar, which promotes tooth decay. George Washington had multiple pairs of dentures over the course of his life. While it would be unthinkable for a U.S. president today to lack teeth, vulnerable populations such as low-income, rural, and marginalized older adults are now far more likely to experience tooth loss. These individuals often face barriers to dental care throughout their lives, from childhood toothaches that kept them out of school, to jobs that did not offer dental insurance.

Compounding these issues, Medicare, the primary insurer for Americans over 65, does not cover routine dental care. A statute in the Social Security Act implemented in 1965 blocks Medicare from covering dental care. My research shows a nearly five-percentage-point increase in missing teeth once individuals lose access to employer-sponsored dental insurance and enroll in Medicare. Today, only about half of adults over 65 visit a dentist annually. President Joe Biden proposed a Medicare dental benefit in his 2021 Build Back Better bill, but it was removed before the legislation passed; subsequent efforts have stalled.

To ensure everyone benefits, dental care must be accessible from childhood onward. Evidence-based strategies to improve oral health include increasing the number of dentists who accept Medicaid, expanding the types of dental services it covers, and adding more dental therapists—professionals similar to nurse practitioners—to the workforce.

Fewer than a third of dentists accept Medicaid, the primary insurance for low-income Americans. In many states, Medicaid offers limited or no dental coverage for adults. The rural dentist workforce, like the rural workforce in general, is aging, and younger dentists are more likely to practice in urban and suburban areas.

> Making dental care affordable for older adults is only part of the solution—care must be accessible from childhood onward.

Even community water fluoridation, the bedrock of dental public health, has come under attack because of concerns about neurotoxicity, even though fluoride in public-water supplies is far below dangerous levels. Fluoridation, which strengthens children's teeth as they form and continues to prevent cavities in adulthood, accounts for much of the progress made in oral health during the 20th century; the baby boomer generation was the first to benefit from fluoride in their water during childhood. Today, many rural communities still rely on well water or other decentralized water sources, which have never been fluoridated.

In the end, the future of oral health may depend less on cutting-edge innovations and more on ensuring that the basics—such as access to fluoride, routine dental care, and affordable treatments—are available to everyone. Our smiles, and our healthspans, could depend on it.

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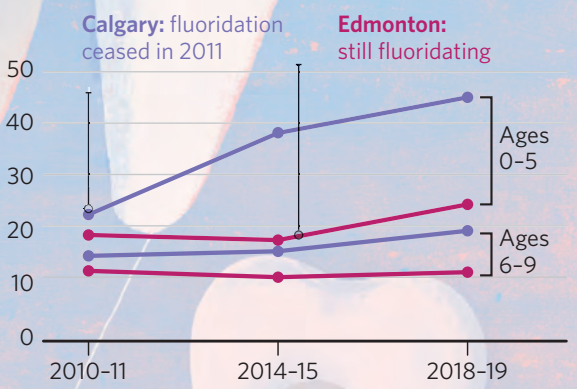
Fluoridation Prevents Cavities

Most U.S. households receive fluoridated water and have since the 1970s, but it has always been controversial. The science, however, is clear: fluoridation prevents cavities—especially in young children, whose tooth enamel doesn't finish hardening until about age 8. One compelling case study comes from Alberta, Canada: after Calgary ceased its fluoridation program in 2011, researchers compared its residents with nearby Edmonton, which continued fluoridating. Children in Calgary clearly saw a jump in cavities not mirrored in Edmonton.

Cavities requiring general anesthesia per 10,000 children



Source: Yazdanbakhsh et al., *Canadian Journal of Public Health*, 2024

The Purposeful Life of Donna Denman

How one woman fashioned a long life of activity and social attachments **BY NEENAH ELLIS | PHOTO BY DENNIE EAGLESON**

An ad appeared last summer in the *Yellow Springs News*, a weekly paper in a southwestern Ohio town of 3,000 people.

"Donna Denman is celebrating turning 90 and is inviting everyone who wants to celebrate with her—or would like to see her pollinator garden—to a Garden Party Celebration. No presents, please, unless it is a poem."

On a perfect July afternoon, under a clear blue sky, three hundred people showed up to admire Donna's garden, read their poems and sing songs to her. They came on foot, by car and on bicycle: friends and family, kids and grandparents.

Donna wanted to show people they can do something about climate change by creating a garden with native plants. People came because Donna is beloved and admired.

Donna has made it to 90, remarkably healthy and active. She's living alone now, but engaged in her town, with her loving family and devoted spiritual community. If you ask her how she did it, at first she says she's surprised to find herself in such good shape. But it's clear that she's made choices all her life that have led her to this enviable place.

Donna is often out and about: in her yard across from the elementary school, at the Senior Center taking a comedy improv class, walking to the Dharma Center for morning meditation, or lifting weights at the Wellness Center with her trainer.

My first memory of Donna is from fifteen years ago. She was on her bike, coasting into traffic at a busy intersection, steady and confident behind her husband, Al, who was also on a bike. The two of them were a matched pair in helmets and reflective vests, slender and strong, heading for town from their home by the nature preserve out on the edge of town. He was in his early 80s; she was 75.

"We decided to ride our bikes as much as possible," she says. "We used our bodies to do things, to save energy. We had a philosophy of using less so there is more for others."

Donna and Al were committed conservationists, both raised in the West by parents who also led healthy, active lives. Donna's mother lived to 97, but genes only get you so far in staying healthy your whole life. Something else is at work.

Before I moved to Yellow Springs, I wrote a book called *If I Live to Be 100: Lessons from the Centenarians,* for which I interviewed more than 30 men and women from all over the U.S. Few of them understood why they had lived so long. I noticed that all of them had something in their lives much larger than themselves, often family or faith. Donna fits that pattern, too, and she is able to explain her life in a way that few others could.

"We decided to ride our bikes as much as possible. We used our bodies to do things, to save energy. We had a philosophy of using less so there is more for others."

Eyes open

Donna grew up in Idaho in the 1930s and 1940s. As a child, she was out one day with her grandfather and brothers shooting gophers and she was accidentally shot. The bullet lodged in her pelvis, and it's still inside her. Her daughter Linnea says surviving that incident moved her to dedicate her life to God and to helping others, and not to focus on herself.

She met Al Denman when she was 16 and married him two years later. He was seven years older. They came to Yellow Springs so Al, a philosopher, could become the pastor and teach law and religion at Antioch College. In the late 1960s they took a trip around the world for his sabbatical, studying world religions. They were committed Christians, but Donna had grown disillusioned with Presbyterianism. On their trip, her eyes opened to Buddhism. She met a Tibetan Buddhist teacher named Chokyi Nyima Rinpoche and learned about the power of meditation. And later on their world tour, they stopped in Kyoto, Japan, where an Antioch College professor intervened on her behalf and special arrangements were made for her to meditate at a Zen temple there, where women were typically not allowed. It was transformational for her.

Back in Ohio, she joined a meditation group. Her practice grew deeper and wove itself into all aspects of her life.

Donna and Al lived simply, she says. In Yellow Springs, everything was nearby: a local grocery store, pharmacy, movie theater, library, and post office. The town had a vibrant, diverse music, theatre and art scene, and an activist student body that enlivened the town and kept it from being a sleepy bedroom community.

Donna's marriage to Al is key to understanding her resilience, says Katie Egart, Donna's friend of more than 30 years, who is now a Zen teacher. Donna looked up to Al, she says, and saw him as her teacher. Their mutual interest in social justice, selflessness and generosity, created a stability that gave Donna the space and structure to explore her own beliefs.

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"You feel you are in touch with ultimate reality. And when you talk about purpose, there's your purpose—to express that."

They raised four children, were active in the community, especially around civil rights, and devoted to the college. Donna worked as a low-income housing specialist for the county. Al passed away in 2022, at the tail end of the pandemic. Donna lives alone now in their house in town.

Most nights her daughter Linnea, who's the town kindergarten teacher, comes over for dinner. She says her mom accepts the changes aging has brought. When her doctor suggested she stop driving, she did, and soon after gave her car away. When it became uncomfortable to sit on a cushion during meditation, she sat on a chair. When her hearing failed, she got hearing aids.

She's not just accepting change, says Linnea, she welcomes it, and she gets excited to learn new things. She's learned to play bridge and mahjong and plays with friends every week. Recently she took up pilates.

"She doesn't stop. She does slow down and things *are* hard for her sometimes, but she always has a way of getting out of it."

Not long ago, says Linnea, her mom met a woman who told her they were depressed at turning 90. "But mom said she was excited about it and was planning a garden party to share what she had learned about the importance of a native plant garden in fighting climate change," says Linnea. "She doesn't stop. She does slow down and things *are* hard for her sometimes, but she always has a way of getting out of it."

Donna's pattern

When I arrive to interview Donna, I follow her into the kitchen, where she has made tea and arranges some cookies on a plate. The living room walls are painted marigold yellow, and tall windows let afternoon light bathe the room with a golden glow. She sits on the couch with perfect posture, her eyes bright and focused. She lets me sit close.

"You know, after the pandemic," she says, "I didn't know what was going to happen because I stayed pretty much at home. After that, I began training with Tron, a local trainer. He and I both were amazed at what I could do. One of the things that really impressed him was the plank." This yoga pose involves holding your body in a straight line, suspended above the floor in an extended push up. "I did a plank, and he counted and counted and counted. I was just amazed—I didn't know I was in good shape."

"I had been in bad shape before then. I'd had a terrible time with sciatica in my back. I never had so much pain. I went to physical therapy, and I felt that it really was helping me. Then a friend told me to do this upside-down thing. I have a table in my room where I can hang upside down. While I was getting better with the physical therapy, somehow hanging upside down just made it faster. So I thought, physical therapy is so important. That's why I wanted a personal trainer."

After a lifetime, she doesn't seem to have created obstacles in her mind.

Her meditation practice, Donna says, has helped her observe herself and her life in a larger context, and over time, her practice has evolved. "What was helpful for me in recent years has been to think of all the people that I care about, and people who are in need, or people who have illnesses, to send loving-kindness, Buddhist practice. You know, 'May they be free from harm, may they be happy, may they be free from suffering and the causes of suffering,' and then saying that about each person. And then I'd fall asleep, which maybe is a good way to fall asleep."

I ask if she thinks her Buddhist journey has an intersection with a healthy life.

"Definitely," she says.

How does it relate?

"Because you learn to relax. And because you feel like you are in touch with something much bigger than yourself. There are different ways to talk about it. But to me, I think, you feel you are in touch with reality, ultimate reality. And when you talk about purpose, there's your purpose—to express that."

Donna is not trying to live long. She is trying to live well. She still walks and bikes and gardens and tells her friends how much they mean to her. After so many years of reflection and practice, the choices are clearer, she says. The values are refined.

Material things, she says—less stuff, less energy consumption—it has become second nature. "You might be sacrificing, "she says, "but you know why."

She and Al shared this way of living, and for a while they seemed ageless. But as Al passed 90, he decided he no longer felt at home in his body. After long discussions with Donna and the family, he decided he had used enough of Earth's resources. He chose to stop eating.

At first Donna said, no, don't do it. But finally she realized, says Linnea, that she had to let him go. He was 91.

At age 90, Donna Denman is a bright light. When you meet her, you can't help but notice that she is radiant.

Neenah Ellis is an independent radio journalist and producer, formerly at NPR and WYSO Public Radio in Yellow Springs, Ohio. Her 2002 book,* If I Live to be 100: Lessons from the Centenarians, *was a* New York Times *bestseller.

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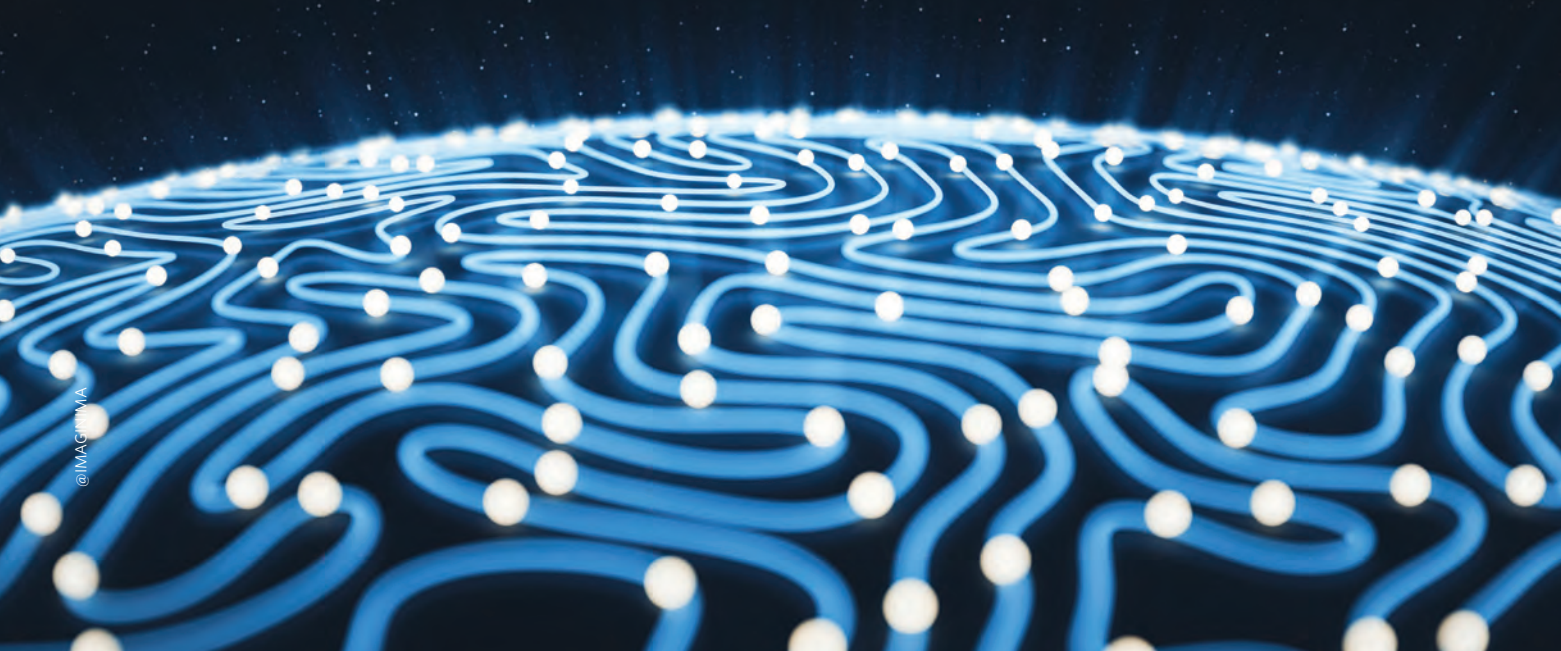

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