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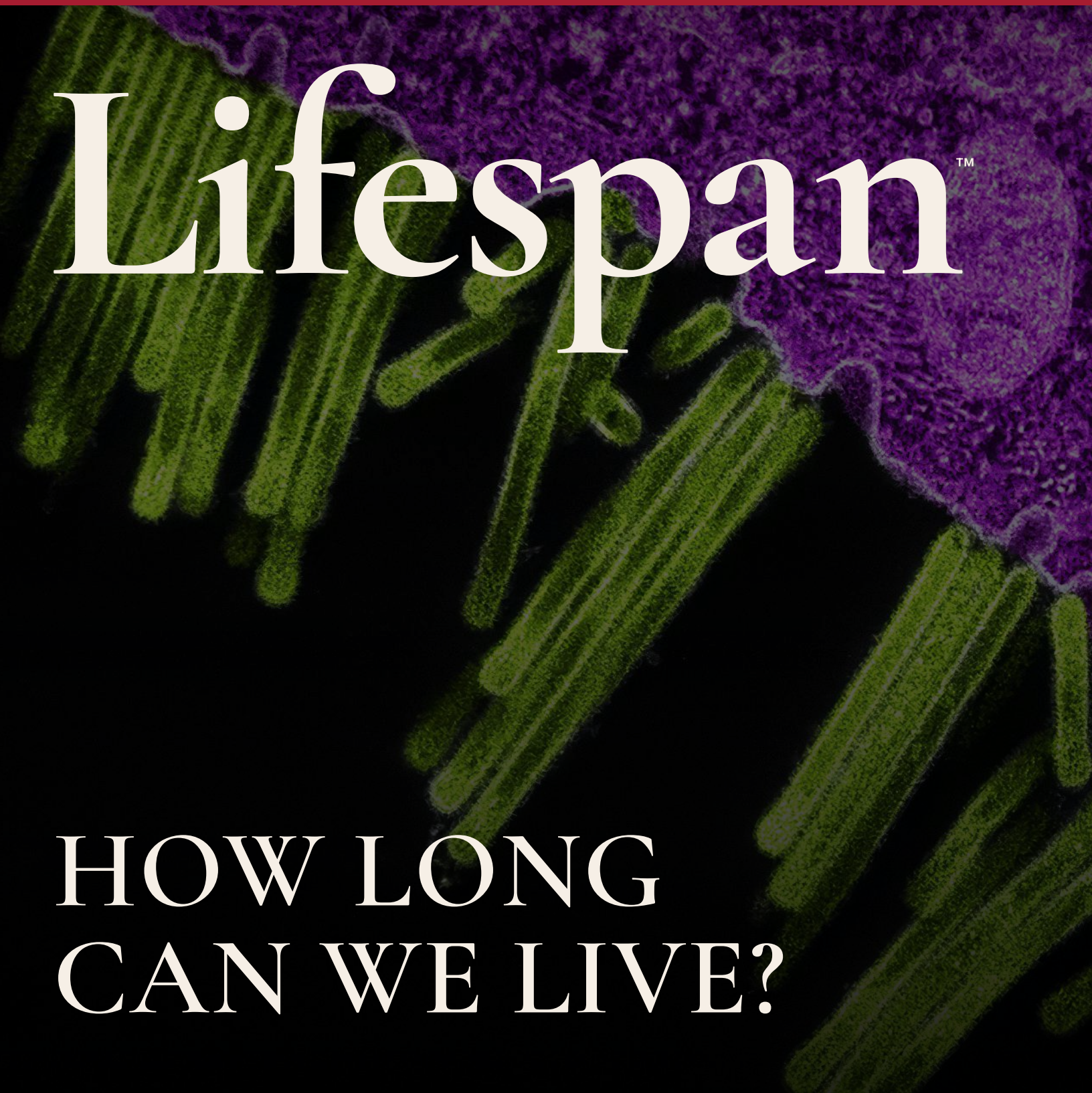
Lifespan™



HOW LONG CAN WE LIVE?

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COVER IMAGE: NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES VIA UNSPLASH
MAGAZINE DESIGN: RYAN MURPHY, HEBA DAGHISTANI

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OPINION

WHY THE GREATEST MEDICAL OPPORTUNITY OF OUR TIME IS PORTRAYED AS A VANITY PROJECT

DAVID A. SINCLAIR, AO, PHD

IMAGE SOURCE: AI-GENERATED WITH OPENAI

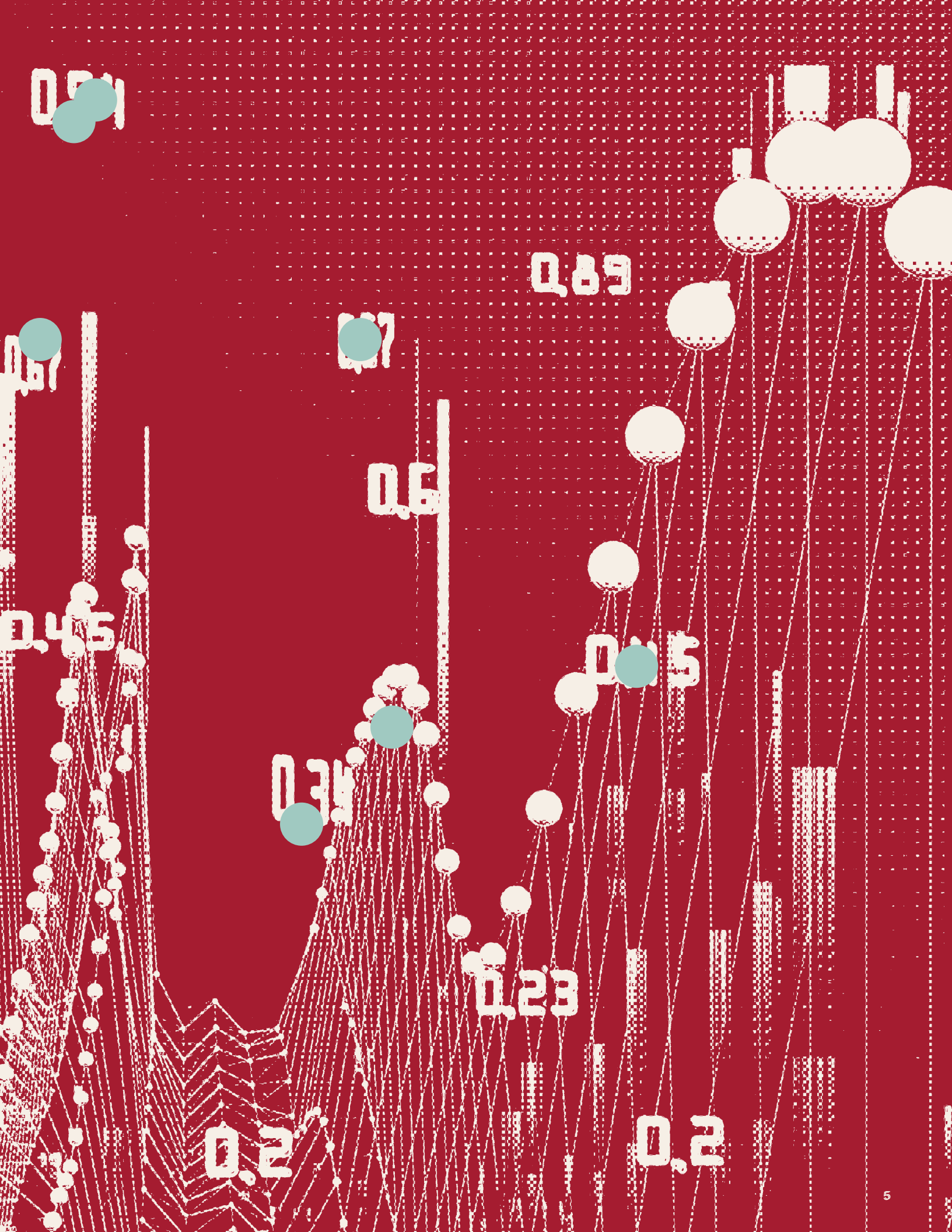
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IMAGE SOURCE: AI-GENERATED WITH OPENAI

Longevity science now occupies that uncomfortable territory between ridicule and inevitability. History repeatedly shows that this is how transformative ideas begin.

Days before the Wright brothers achieved powered flight in December 1903, *The New York Times* suggested that flying machines belonged in the "realm of impossibility" and might take another "million years" to invent. Human flight sounded fantastical, unserious, perhaps even fraudulent. Critics mocked the idea, and the media amplified the skepticism. Then, almost overnight, the impossible became inevitable.

Motorized planes were dismissed as unrealistic, mocked as hype, or treated as curiosities before eventually becoming obvious in retrospect. Looking back, we can clearly see that reporters and editors of the time failed to recognize that, underneath the noise, something profound was happening.

Over the last decade, public discussion about aging research has been more of cultural commentary and clickbait than a thorough examination of the science.

Doctors on social media bring their own biases, incentives, and occasionally a degree of schadenfreude. Reporters often portray longevity science as an overhyped playground for wealthy technologists terrified of death, fueled by supplements, vanity, and fantasy. It is an easy caricature to sell. Fascination with obsessive rich eccentrics chasing impossible dreams is no less prevalent today than it was in 1903.

Some people in the longevity world are unquestionably selling interventions that are unproven, exaggerated, or even dangerous. They deserve scrutiny. But it is equally important to distinguish commercial hype from genuine scientific progress.

Scientists who speak publicly about advances in aging research, or who dare to speculate carefully about where the science may be headed, are often misquoted or caricatured. Nuance rarely survives the modern media cycle. Complex scientific questions are flattened into easy narratives about "immortality," "anti-aging gurus," and "snake oil," because those stories are simpler, more provocative, and more likely to travel.

Not that criticism isn't welcome. It is essential to science. Claims must be challenged rigorously, repeatedly, and in public. But skepticism loses its value when it becomes an inability to adapt to change or recognize real progress.

Longevity science is not, at its core, a quest for immortality. It is an effort to prevent suffering: to delay or reverse blindness, frailty, dementia, cardiovascular disease, diabetes, and many other chronic conditions that become more common with age. The goal is not simply to add years to life, but to extend the years spent healthy, capable, mentally sharp, physically mobile, and independent. That matters because most people do not fear death as much as they fear decline.

They fear losing their eyesight, their memory, their mobility, and their dignity. They fear becoming dependent on others, cognitively diminished, isolated from the world, or unable to recognize the people they love.

Modern medicine has traditionally treated these conditions one at a time: one drug for diabetes, another for heart disease, another for Alzheimer's disease. Aging biology suggests a deeper possibility. Many of these diseases may arise, at least in part, from shared biological mechanisms associated with the aging process itself. This idea lies at the heart of modern geroscience.

Young organisms are resilient for a reason. Their cells repair damage efficiently. Their tissues regenerate. Their immune systems respond robustly. Their epigenetic programs preserve cellular identity and function. With time, these systems begin to fail. If the processes driving that deterioration can be slowed, repaired, or partially restored, then medicine changes at a fundamental level.

What once sounded like a provocative hypothesis is now being tested experimentally in laboratories around the world. Aging biology has moved from the scientific margins toward the mainstream. Over the past three decades, the field has progressed from studies in yeast, worms, and flies, to demonstrations that many mechanisms controlling longevity are conserved in mammals, and now toward the much harder task of translating those discoveries into human therapies.

Today, scientists can estimate aspects of biological age using DNA methylation clocks with striking accuracy. Senescent cells can be selectively removed in animals, improving tissue function and, in some studies, extending lifespan. Biological mechanisms involving mTOR, AMPK, insulin signaling, NAD+ metabolism, and sirtuin proteins have repeatedly been shown to influence aging across species.

These are not internet theories. They emerge from decades of peer-reviewed research in journals such as *Cell*, *Nature*, and *Science*, including work from my laboratory and many others. Studies have shown, for example, that restoring aspects of epigenetic information can recover lost function in aged and damaged retinal tissue in mice, with related findings extending into non-human primates. Our initial work was published in *Nature* in 2020[I] and has since been expanded by other laboratories and by companies pursuing translational therapies.

And yet, despite this progress, much of the public conversation about longevity remains strangely unserious. Researchers are sometimes discussed as though they were invoking ancient myths rather than testing molecular hypotheses with modern experimental tools.

There is an irony here. Society celebrates efforts to cure cancer, prevent Alzheimer's disease and restore eyesight. Yet discomfort often appears when scientists suggest that several of these conditions may share underlying biological drivers connected to aging itself.

The objection is sometimes scientific, and it should be. But some of it is philosophical. Just because aging has accompanied every human life throughout recorded history, it doesn't mean we have to accept its cruelty. We must not confuse what is universal with what is unchangeable.

"History rarely remembers the cynics. It remembers the moments when medicine expanded the boundaries of what was thought possible."

History suggests that is a dangerous assumption. Many biological limits once regarded as permanent remained so only until science learned how to intervene. Childhood mortality was once considered inevitable, as was surgical pain and infectious disease. Tooth decay, maternal death during childbirth, and cervical cancer were all once accepted as unavoidable features of life. Medicine exists because humanity refuses to accept unnecessary suffering simply because it has always existed. What makes aging

biology uniquely provocative is that it challenges one of the oldest assumptions in human civilization: that decline itself may be biologically modifiable. Some scientists remain uncomfortable even discussing aging as a treatable process. Interestingly, many of these same critics already support interventions that extend healthy lifespan indirectly through exercise, dietary interventions, blood pressure control, GLP-1 receptor agonist drugs, statins, smoking cessation, and metabolic therapies.

The disagreement is often not about whether healthy lifespan should increase. It is about whether society is prepared to conceptualize aging itself as biologically malleable.

Paradigm shifts rarely arrive gently

Professor Max Planck once observed in his autobiography, written in his native German, that "a new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents gradually die out." The quote endures because it captures something deeply human about scientific institutions. Scientists are trained to be skeptical, and rightly so. Skepticism is essential to the scientific process. But at times, healthy skepticism can harden into resistance, particularly when new ideas challenge established frameworks, careers, or assumptions.

Modern media, both legacy and social, amplifies this tendency because conflict is compelling and nuance rarely attracts attention as effectively as controversy, hype, or personality-driven narratives. The result is that emerging fields are often judged less by the quality of the underlying science than by the caricatures built around them.

The irony is that many medical breakthroughs now regarded as obvious, even heroic, endured years or decades of ridicule before succeeding clinically. Organ transplantation was once dismissed as grotesque and impossible. In vitro fertilization was condemned as unethical and unnatural. Gene therapy suffered devastating setbacks before eventually producing life-saving treatments. Some prominent scientists initially rejected the idea that AIDS was caused by a virus. Cancer immunotherapy spent decades at the fringes of medicine before becoming transformative.

Even Dr. Stanley Prusiner, who later received the Nobel Prize for discovering prions, the infectious proteins behind Mad Cow disease and related brain disorders, spent years defending what many scientists initially regarded as a heretical idea and was so upset he stopped talking to reporters for a decade.

Yes, the field contains over-promisers and over-promises. Every emerging scientific discipline attracts opportunists: nutrition, stem cells, neuroscience, psychedelics, and even AI have been accompanied by waves of hype. But exaggerated claims do not invalidate the underlying science.

IMAGE SOURCE: LOGAN GUTIERREZ VIA UNSPLASH

"Most people are not afraid of death nearly as much as they are afraid of decline. They fear losing their eyesight, their memory, their mobility, their dignity."

IMAGE SOURCE: SK VIA UNSPLASH

The better responses to hype are scientific and investigational rigor, not cynicism.

One of the more common criticisms leveled against longevity science is that it represents a luxury obsession for wealthy people attempting to avoid mortality. But this criticism ignores both economics and history. Nearly every transformative medical technology initially benefited wealthier populations before eventually scaling broadly across society. Genome sequencing once required billions of dollars and international collaborations. Today it can be performed for a few hundred dollars and will only get more affordable.

Innovation nearly always begins unevenly before becoming democratized. Organ transplantation and cancer immunotherapy were both initially expensive, limited, and relatively inaccessible. The ethical solution to inequality is not to suppress innovation. It is to expand access. Rejecting advances in aging research does not create fairness. It simply preserves suffering more equally.

Another criticism is that extending lifespan would worsen overpopulation or strain economies. But this misunderstands what longevity science is trying to achieve. The goal is not simply extending years of frailty. It is compressing morbidity – reducing the period of sickness and disability before death. A healthy 85-year-old who remains mentally sharp, physically active, and socially engaged contributes very differently to society than someone spending years in chronic disease and institutional care.

The economic implications of extending lifespan are enormous. Healthcare expenditures in developed nations are heavily concentrated during the final years of life, particularly during prolonged periods of chronic illness. Analyses published in *Nature Aging* estimate that even modest increases in healthy lifespan could generate economic gains on the order of tens of trillions of dollars in the United States alone.[2] This concept has become known as the "longevity dividend".[3] Healthy older adults are not merely consumers of resources. They are caregivers, educators, scientists, artists, entrepreneurs, mentors, and sources of social stability.

Modern civilization was built around a biological reality in which humans experienced relatively brief, healthy adulthoods followed by decline.

We educate intensely during youth, work for several decades, then often spend years coping with disease and frailty. But if healthy lifespan expands substantially, human life itself becomes structurally different.

People may pursue multiple careers. Return to education repeatedly. Become parents later in life. Reinvent themselves in their 60s or 70s rather than viewing those decades as a gradual withdrawal from relevance. I have publicly discussed one possible future concept as a "skillbatical," periods of retraining and reinvention distributed throughout life rather than compressed entirely into youth.4

I think about my father every day, then I call him. At 86, he remains intellectually engaged, socially connected, physically active, and deeply curious about the world. He exercises, sleeps well, prioritizes relationships, eats thoughtfully, and embraces evidence-based approaches to maintaining health. He is living healthier and happier in his 80s than in his 40s.

My father is no longer unusual. Around the world, millions of older adults are demonstrating that later life can remain productive, meaningful, and vibrant far longer than previous generations assumed possible. This is the future longevity science is trying to build. Not immortality. Vitality.

Meanwhile, laboratories around the world are restoring vision in animals, identifying cellular aging clocks, developing senolytic therapies, engineering immune systems, mapping cellular states with unprecedented precision, and using artificial intelligence to accelerate therapeutic discovery. I am one scientist, at one institution. I am part of a far-reaching field of longevity science that stretches across disciplines and around the globe.

For the first time in human history, scientists can seriously ask not merely why organisms age, but whether aspects of aging can be biologically restored. The answer once belonged entirely to mythology. With modern molecular tools, it belongs to science.

Healthcare systems, insurers, regulators, employers, and governments are still largely unprepared for a world in which people could remain healthy and productive decades longer than previous generations. Preparing for that future will require thoughtful engagement across medicine, economics, ethics, public policy, and culture.

One day, I suspect society will look back on this era much as we now look back on earlier turning points in medical history. People will wonder why attempts to treat blindness, frailty, dementia, and other age-related conditions were once dismissed as fantastical. They will ask why preserving human vitality and independence was ever considered unserious.

Part of why I created *Lifespan Magazine* was to help disseminate thoughtful, evidence-based information about longevity science to a broader public audience. If you are skeptical and reading this, good. Skepticism is valuable. I only ask that you continue reading with an open mind about what may become possible as science advances.

The claim that longevity science is merely hype, or a vanity project for the wealthy, persists because cynicism is easy. There is a certain emotional satisfaction in dismissing ambitious ideas before they succeed. History, however, rarely remembers the cynics. It remembers the moments when medicine expanded the boundaries of what was thought possible.

Longevity science is not about denying death or escaping our humanity, as critics and reporters often portray it. It is about reducing suffering by preventing frailty, blindness, dementia, cancer, and the slow loss of independence that so many people witness in their parents before experiencing it themselves. In the end, the goal is not merely to add years to life. It is to preserve vitality, dignity, and time with the people we love.

That's not hype. It's medicine's next frontier.

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FOUR NEGOTIATIONS EVERY MAN HAS WITH TIME

IMAGE SOURCE: MIDJOURNEY

BY KELLY RICH, MS, CGC, PHD

“Men don’t get a menopause. What they get, repeatedly, are negotiations with time.”

IMAGE SOURCE: ANDREYBILING VIA ADOBE STOCK

In last month's issue, I wrote about women's aging through the lens of ovarian shutdown. Menopause is often framed as a cliff: one organ changes its behavior around 50, the rest of the body scrambles to adjust, hot flashes abound. Most men have seen their wife, sister or mother experience the night sweats, mood swings, and brain fog that seemed to cluster around midlife. You rarely know the exact day it will all start, but most women can look back and say, "Around 49," or "Right after I turned 52, everything changed." Men read that and asked a different kind of question. It isn't "When is my cliff?" so much as "How long can I keep what I have?"

Women, for all the misery menopause can bring, at least have a name and a flag for this transition. "I'm perimenopausal" or "I'm postmenopausal" has become a socially legible way for women to say: my body is reorganizing itself, please expect changes. Men's biology has no equivalent sequence. Puberty arrives and then, hormonally speaking, the rest of life is one very long chapter. There is no age at which you can say, in one word, "This is the phase I'm in." Instead there are scattered hints – a lab result from your doctor, a new prescription, an uptick in bathroom trips – and a vague expectation that you should somehow fight to stay the same without a clear script for what "the same" would even look like.

For the average man in his 50s, 60s, or 70s, aging shows up as small erosions: a bit less power in your legs, a slower recovery after lifting, erections that are more negotiation than reflex, a softening waistline, a prostate-specific antigen number you never used to know (or care) about. Men notice that they can no longer do, automatically and invisibly, what many built their adult lives on: carry heavy groceries, work a twelve-hour day, sleep through the night, count on their bodies to respond on demand. The loss can feel both physical and reputational. If you have spent fifty years being the person who can fix the thing, carry the thing, and perform when it matters, then each moment when your body doesn't quite deliver can feel like a small revision of identity.

That difference also explains why my article on women's aging barely mentioned sex. For women, the organizing story was an organ that times the whole transition (the ovary), and sexual changes fit inside that larger architectural shift. For men, sex, strength, and stamina are not side notes, they are front and center. Writing about how those things change with age can feel awkward, in part because we still treat male sexual function as a referendum on character rather than as a biological system that ages like any other. When men ask about testosterone, hair loss, prostate tests, or nighttime urination, they are not only asking medical questions. They are asking how long they can inhabit the roles they know themselves by (worker, partner, protector, athlete-*ish*) before the body edits their script.

Men don't get a menopause. What they get, repeatedly, are negotiations with time. You don't negotiate from a blank slate. The last few decades of sleep, work, food, illness, and exercise set the opening offer. But in four domains – desire, strength, sleep, and certainty – the data suggest that how you respond still matters. You cannot win every negotiation. You can, however, show up prepared.

Negotiation 1: Desire vs. time

For men, some negotiations tend to collect themselves around testosterone – which has become shorthand for energy, drive, and even identity. Testosterone plays a starring role in the way men imagine aging. It is the hormone behind insults ("low T" as a lazy shorthand for weakness), the fuel in gym folklore, the molecule that underground labs

promise to "optimize." Increasingly it is also a cultural symbol. Podcasts, social media feeds, military leadership and direct-to-consumer testosterone "clinics" hold it up as a kind of all-purpose upgrade for being a man, blurring the line between a real medical treatment for real testosterone deficiency and a product meant to signal status, masculinity, or belonging.

Biologically, testosterone is less of a cliff than a slope. Total testosterone is the entirety of this hormone circulating in the blood, while free testosterone is the small fraction not tightly bound to carrier proteins and most readily available to tissues. In large population studies, total testosterone declines by roughly 1-2% per year after midlife on average, and free testosterone often falls faster as more of the hormone gets tied up.[1–3] Yet if you line up hundreds of men between 40 and 80 and measure their hormones, you do not see a clean, perfectly descending staircase by decade; there is wide overlap between age groups. Men in their seventies can have higher testosterone levels than some men in their fifties. Some with "low" values on their lab reports sleep well, think clearly, train, and have satisfying sex. Others with similar numbers feel blunted, with less drive, less physical capacity, less pull toward intimacy.

When a biomarker tends to decline with age, it is tempting to imagine that "more" must offer protection. Large cohort studies and meta-analyses have asked whether higher testosterone keeps you alive longer. When researchers plot testosterone against mortality across tens of thousands of men, they do not see a line slanting neatly downward, indicating more hormone, fewer deaths. What appears instead is a curve. The risk of death rises mainly when testosterone drops into clearly low territory.

Men with very low levels of T are more likely to die, especially of cardiovascular causes, but men with middling or high-normal levels do not seem to buy extra survival simply by sitting on the upper end of the range.[4,5] Very low testosterone also tends to show up alongside diabetes, obesity, and other chronic disease, making it as much a read-out of overall health as a driver. Part of that association likely reflects biology – severe androgen deficiency can worsen body composition, insulin resistance, anemia, and cardiovascular risk – and part of that reflects confounding variables because serious illnesses, chronic inflammation, and long-term stress all tend to push testosterone down.

"Large cohort studies and meta-analyses have asked whether higher testosterone levels keep you alive longer."

That background makes it easier to understand a different set of headlines: claims that men as a group are becoming "low T" compared with previous generations. There is some truth to that, but the signal is easy to misread. A large share of the population-level drop appears to track with gaining more weight, moving less, sleeping worse, and carrying more chronic stress, not with a sudden, mysterious collapse of the male endocrine system. For many men whose numbers sit in a gray zone, losing a modest amount of weight, fixing sleep apnea, and lifting regularly will raise testosterone enough to move them out of the "borderline" category, often without a prescription.

For many men, this all stays abstract until one particular thread starts to fray: libido. Not just "I don't want sex as often," but "I don't want sex at all." Historically, medicine has been cautious about using testosterone here. Official indications were limited to "classical" hypogonadism

(testicular failure from genetic syndromes or clear structural damage) and guidelines discouraged treatment of men whose only problem was age-related decline in libido.

Over the last decade, that stance against using testosterone mid-life has softened thanks to better trials.[6-9] Randomized studies in middle-aged and older men with low or low-normal testosterone show that replacement therapy produces modest but consistent improvements in sexual activity, desire, and overall sexual function compared with placebo, with smaller gains in erectile rigidity itself. Men on treatment often describe wanting sex more and feeling somewhat more reliable, without being transported back to their twenties.

Regulators are starting to catch up to that reality, too. In 2025 the FDA signaled it was considering a new indication for testosterone products: treatment of low libido in men with low testosterone without a known structural cause (called idiopathic hypogonadism) on the grounds that diminished sexual desire is clinically meaningful, measurable, and directly linked to testosterone biology.

IMAGE SOURCE: RADOSNASOSNA VIA ADOBE STOCK

That move reflects what doctors have observed for decades: for some men, particularly those whose relationships are being strained by loss of desire, libido is where the negotiation with time feels most urgent.

The negotiation here is straightforward and personal. Does a loss of desire bother you, and how much? Are your levels repeatedly low on high-quality tests, after obvious reversible factors (medications, acute illness, profound sleep deprivation) have been addressed? Are you willing to accept injections or gels, regular lab monitoring, and small but real risks like thicker blood (testosterone commonly raises red-blood-cell counts and hematocrit), unmasking pre-existing prostate disease, or a slightly higher chance of atrial fibrillation or pulmonary embolism, as seen in the TRAVERSE trial?[10] If you answered "yes" to these questions, then testosterone is a reasonable ally. It is not magic, and trials show only slight improvements in overall mood and depressive symptoms.[9,11] But for many men, recovering and maintaining sexual desire is a primary goal of aging well.

Negotiation 2: Strength vs. effort

Ask men what they fear losing most as they age and strength appears quickly, sometimes coded as "I don't want to be frail" and sometimes explicit: "I still want to be able to pick up my grandkids." It is enticing to fold this entirely into testosterone – if the hormone builds muscle, why not let the prescription do the heavy lifting?

Testosterone, once again, is not a magic cure for loss in strength. Sarcopenia, the age-related loss of muscle mass and strength, starts earlier than most men realize and accelerates with inactivity. Leg power, grip strength, and gait speed strongly predict future falls, disability, hospitalization, and mortality. On

those outcomes, the squat rack and the walking trail are more valuable than testosterone will ever be.

To be fair, testosterone replacement can help. Across randomized trials in older men with low or low-normal levels, treatment increases lean mass and strength, with the largest effects seen when testosterone is given by intramuscular injection rather than as a transdermal gel or patch.[12–14] Injections create higher peaks in blood levels, and that surge appears to drive more muscle response. But the overall gains are modest. Meta-analyses suggest small effect sizes for strength, and in the Testosterone Trials – a coordinated set of NIH-funded studies in men 65 and older with low testosterone – increases in walking distance and physical performance were measurable but not transformative.[9]

"Testosterone helps, but it does not substitute for work."

When researchers directly compare testosterone to exercise, or combine them, the ranking is clear. In studies where older men with low-normal testosterone are randomized to exercise training (progressive resistance and aerobic training), testosterone therapy, both, or neither, the biggest improvements in strength and aerobic fitness come from training, not from testosterone alone.[15,16] Adding testosterone on top of a solid exercise program mostly adds extra lean mass and slightly higher strength without consistently improving walking speed, stair climbing, or other real-world performance beyond what training already provided. Testosterone helps, but it does not substitute for work.

The relationship between exercise and testosterone adds another twist. Systematic reviews of men over 40 show that resistance training, endurance exercise, and high-intensity interval training can all nudge basal testosterone up modestly, especially with high-intensity interval training and endurance protocols.[17–19] Yet in those same studies, men gain muscle, lose fat, and improve function even when their testosterone scarcely budges. Only when researchers pharmacologically suppress testosterone into clearly hypogonadal ranges do gains in strength and hypertrophy (bigger muscles) become impaired.[20] Within the normal or low-normal range, the main limiting factors are load, volume, recovery, and whether you continue to show up.

Mechanistic work supports this. Hypertrophy tracks more closely with what happens inside the muscle – activation of satellite cells, mTOR signaling, androgen-receptor content – than with modest swings in circulating testosterone.[21] Your tissues are listening most closely to mechanical stress, not to the hormone itself.

The second negotiation, then, is less glamorous and more brutal: How much effort are you willing to trade for strength? Testosterone can sweeten the bargain if you are clearly deficient and symptomatic, but it cannot replace the fundamental exchange of time, discomfort, and consistency for muscle and function. For many men, the fair deal looks like this: use testosterone, when truly indicated, to make training more productive and life more enjoyable, but accept that dumbbells, hills, and brisk walks are still doing the heavy lifting.

Negotiation 3: Sleep vs. the prostate

If testosterone is the health subject men talk about the most, the prostate is the one they avoid. Benign prostatic hyperplasia (BPH), is close to a default outcome of living long in a male body. By their 60s, about half of men have histologic evidence of an enlarged prostate. By their 80s, that figure is closer to 80%.[22] Not all that growth translates into symp-

IMAGE SOURCE: RAWPIXEL.COM VIA ADOBE STOCK

toms, but enough that lower urinary tract symptoms – weak stream, hesitancy, frequent urination, incomplete emptying – become a defining irritation of older male life.

Waking multiple times per night to urinate (known as nocturia) can be deeply corrosive. Midnight bathroom trips chip away at sleep, cognition, mood, and relationships in a way daytime frequency does not. In large registries of men over 50 with BPH-related symptoms, roughly two-thirds report clinically-significant nocturia, with prevalence rising sharply after age 70.[23] Yet the gland does not act alone. The same midlife villains that hurt the heart – obesity, metabolic syndrome, hypertension, sedentary behavior – also show up with larger prostates and worse urinary symptoms.[24] The prostate is plugged into the same metabolic network as the rest of the body.

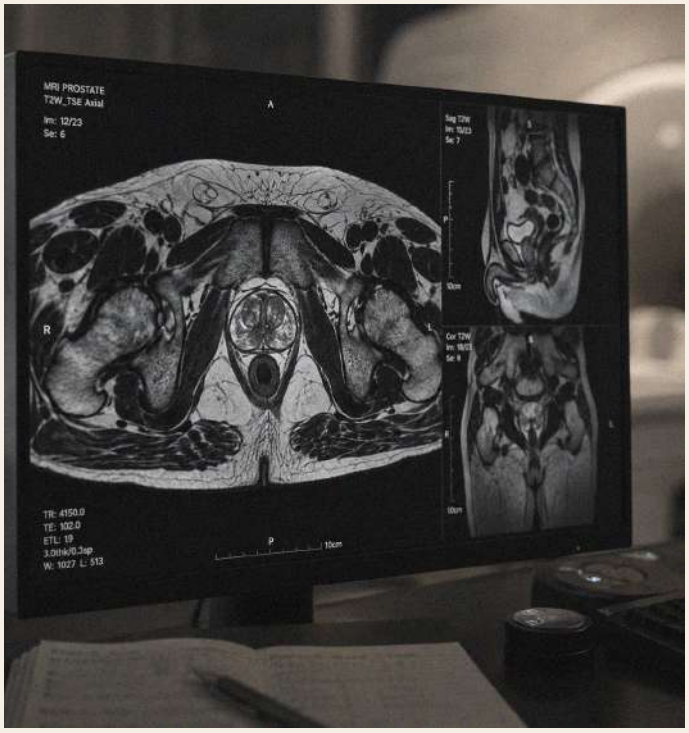

IMAGE SOURCE: AI-GENERATED WITH OPENAI

The unmedicated natural history is slower than many men fear. On average, the prostate gland increases in volume by a couple of percent per year, symptom scores tend to inch upward over four or five years, and only a small minority progress to complete urinary retention or need surgery. That leaves a wide window for adjustment. Lifestyle measures matter here: limiting evening fluids and caffeine, moderating alcohol, and using bladder-training or pelvic-floor techniques can reduce the frequency of urination and urgency, while physical activity and weight loss modestly ease symptoms and may slow progression.[25]

When behavior is not enough, medications become part of the negotiation. Alpha-blockers relax smooth muscle in the prostate and bladder neck, improving flow and symptom scores within days or weeks. They don't shrink the gland but often make life more livable. 5-alpha-reductase inhibitors such as finasteride and dutasteride lower dihydrotestosterone in the prostate, shrink the gland over months, and reduce the risk of acute urinary retention and surgery in men with enlarged prostates.[25] Combining the two approaches works best for men with sizable glands and bothersome symptoms, cutting progression risk roughly in half in large trials.[26] Over-the-counter supplements rarely live up to marketing. Saw palmetto performs no better than placebo in trials, and other supplements show, at best, small symptomatic improvements without current evidence that they change long-term outcomes.[25] Taking glycine, for example, has shown promise for sleep quality in small studies, largely by helping to lower core body temperature,[27–29] but the evidence is early and larger trials are needed.

This negotiation is about trade-offs between sleep, side effects, and effort. Some men accept two bathroom trips a night and tweak fluid intake. Others trade dizziness from an alpha-blocker or potential side effects from a 5-alpha-reductase inhibitor for uninterrupted sleep. A smaller group chooses minimally invasive procedures or surgery. BPH, unlike ovarian shutdown, offers options and time to consider them. The price is that there is no obvious moment when everyone agrees it is time to act.

Negotiation 4: Certainty vs. screening

The same small gland that causes benign enlargement and nighttime urination is also the source of something more ominous: prostate cancer. Statistically, it is among the most common cancers men will face. Many tumors are so slow-growing that a man is more likely to die with prostate cancer than from it, though a smaller fraction is aggressive and life-threatening. The central question in screening is how to tilt the odds of catching the dangerous ones early without flooding the system with false alarms and overtreatment.

Prostate-specific antigen (PSA), has been at the center of that debate for three decades. Large, randomized trials and meta-analyses now give a reasonably stable picture: regular PSA screening modestly reduces deaths from prostate cancer – roughly one death prevented per about 1,000 men screened over 10-13 years in major trials – but does not change overall mortality.[30,31] Those saved lives come at the cost of overdiagnosis: more indolent cancers found that never would have caused symptoms, more biopsies, and more men living with incontinence or erectile dysfunction after treatment for tumors that might never have mattered.

Modern guidelines respond by threading a narrow path. Most recommend that average-risk men consider PSA testing, if at all, between ages 55 and 69, and only after a real conversation about benefits and harms. Routine screening is generally discouraged beyond 70 or in men with limited life expectancy.[32] Men at higher risk, due to strong family history, certain genetic variants, or ancestry, may appropriately start earlier and screen more often.

While there is a lack of consensus about genetic testing recommendations in prostate cancer,[33] most guidelines recommend genetic testing for men with high risk disease (high-risk local or any metastatic prostate cancer) regardless of family history, for those with certain personal or family histories of cancer, and for men of Ashkenazi Jewish ancestry. Somatic testing (genetic testing of the tumor itself) is advised for men with hormone-sensitive or castration-resistant metastatic prostate cancer. For men with localized disease, genetic testing is generally reserved for situations where results are likely to influence treatment, clinical trial options, management of other cancer risks, or cascade testing in relatives. For men without prostate cancer, most guidelines stop short of broadly recommending genetic testing, though the National Comprehensive Cancer Network supports germline testing when family history suggests a hereditary cancer syndrome.

What happens after an abnormal PSA has evolved as much as whether to test in the first place. In the early PSA era, an elevated value often led straight to a biopsy, involving a needle sampling the gland somewhat blindly. That approach amplified overdiagnosis and still missed some aggressive tumors. Current pathways layer in other tools. Blood panels such as the Prostate Health Index and 4Kscore refine risk estimates, while multiparametric MRI of the prostate helps identify lesions likely to be clinically significant and guides targeted biopsy, reducing unnecessary procedures and detection of very low-risk disease.[34,35] Gleason scores, which grade how abnormal prostate cancer cells look under the microscope, and clinical risk tools such as D'Amico or CAPRA that combine PSA, tumor stage, and biopsy findings remain central to risk stratification. Increasingly, they are complemented by genomic classifiers like Decipher, which analyzes the expression of RNA markers in the tumor to better predict an individual man's risk of metastasis or death and help tailor decisions about surveillance, surgery, and radiation. Active surveillance – structured monitoring with PSA, imaging, and periodic biopsy – has become the default for many low-risk tumors, allowing men to defer or avoid radical treatment unless the cancer shows signs of waking up.

Digital rectal examination (DRE), once ritualized as part of every annual physical, has turned out to be far less useful than its cultural weight suggests. Contemporary studies show that, in asymptomatic men, DRE detects very few additional cancers beyond what PSA and imaging already reveal, and meta-analyses find little added predictive value.[36,37] Many expert groups no longer recommend routine DRE as a stand-alone screening tool for average-risk men.

This fourth negotiation is about appetite for certainty versus tolerance for collateral damage. Some men sleep better choosing not to screen, accepting that they might miss a slow-growing cancer and, rarely, a dangerous one. Others prefer to carry the risk of false alarms and side effects rather than the risk of undetected progression. The point is not to steer everyone to the same choice, but to make the trade-offs visible so the choice is deliberate.

The work of staying yourself

Taken together, these four negotiations – around desire, strength, sleep, and certainty – sketch a version of male aging that is less about sudden catastrophe and more about maintenance. There is no male equivalent of ovarian shutdown. Instead, midlife and later life in a male body look like a set of curves that can be shifted but not flattened: gradual hormonal drift, slow erosion of muscle and aerobic capacity, steady enlargement of the prostate, rising baseline cardiovascular risk, an increasing chance of microscopic cancers. Across the high-quality trials and cohort studies, the same levers surface again and again.

Testosterone replacement can help if you are truly deficient and suffering, especially with libido and sexual function, and it appears largely neutral to heart health over the short to medium term when given at physiological doses, though arrhythmias and thromboembolism are somewhat more common. It is not a cure-all, it is a targeted tool.

Exercise turns out to be the closest thing men have to required maintenance. Regular, progressive resistance training plus steady aerobic work supports almost everything that most men say they care about in later life: strength and mobility, better insulin sensitivity, healthier blood pressure, more resilient brain function, even slightly better urinary symptoms at the margins.[15,19] The same is true for basic metabolic and cardiovascular control. How well you manage blood pressure, LDL cholesterol, blood sugar, smoking, and sleep apnea does more to determine whether you reach 90 walking unaided and thinking clearly than any single hormone level or supplement ever will.

The prostate is a small, strategically placed structure that will almost certainly demand attention as you age. BPH and nocturia are common and usually manageable. Prostate cancer is common but, with modern risk-adapted screening and active surveillance, increasingly treatable in ways that reflect what we know about tumor behavior. The questions are when you choose to engage, with which tools, and with what tolerance for side effects and uncertainty.

None of this is meant to minimize the real struggles men face. Men die younger than women, are more likely to die of overdose or suicide, and are less likely to seek help for depression or chronic pain. It is understandable that a simple-sounding intervention like testosterone can feel like a way to reclaim energy, mood, and a sense of self. But hormones alone cannot substitute for the foundations of men's health. There is no romantic narrative to hang on this, no single "man-opause" moment around which to build a rite of passage. There is only the steady work of preserving capacity: keeping muscle, power, and endurance high enough that the inevitable losses land you at 80

closer to “a slower version of my 50-year-old self” than “unrecognizable.”

Testosterone, prostate-screening decisions, medications for nocturia – all of these are important clinical tools. The heavy lifting is still blood moving through compliant arteries, muscles that can generate force on demand, lungs that can feed them, and a brain that still wants to use them. It’s tempting to think that the right lab number or the right injection can hold the line against time. The truer story is that male aging is a series of negotiations you can’t entirely win, but you can come to each one prepared.

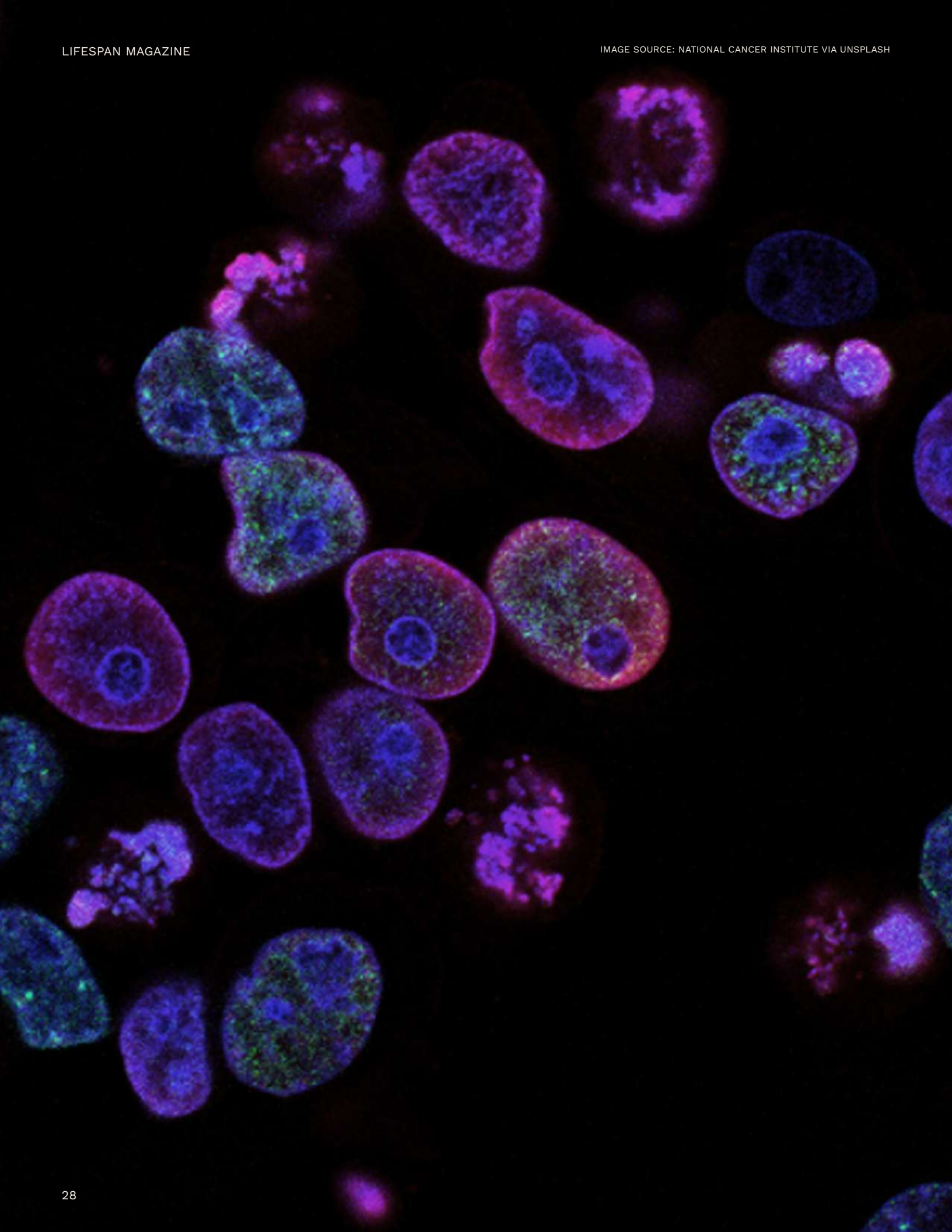

IMAGE SOURCE: NATIONAL CANCER INSTITUTE VIA UNSPLASH

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OPINION

HOW LONG CAN WE ACTUALLY EXPECT TO LIVE IN THE COMING YEARS?

BY ADIV JOHNSON, PHD

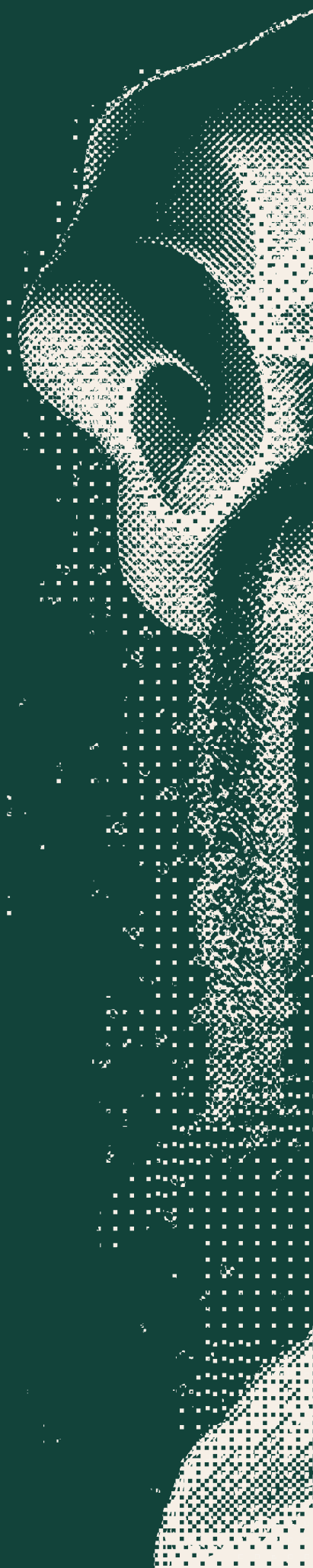

IMAGE SOURCE: AI-GENERATED WITH OPENAI

A field prone to hype

Most longevity or wellness enthusiasts have heard of things like free radicals or oxidative stress. Perhaps you've seen supplements or foods labeled with "antioxidants" or actively seek out antioxidant-containing products.

The idea that antioxidants are important for aging can be traced back to an influential paper that came out 70 years ago.[1] In 1956, Dr. Denham Harman published a seminal paper in the *Journal of Gerontology* titled "Aging: A Theory Based on Free Radical and Radiation Chemistry." Today, this paper has more than 10,000 citations and represents one of the most impactful publications in the field of aging.

Dr. Harman's paper outlined the idea that aging and all of its undesirable manifestations are due to the damaging effects of something called free radicals. A free radical is any molecule, ion, or atom that contains an unpaired electron and is thus highly reactive with other chemicals. It's like an energetic, untrained dog at a party that really likes to interact with strangers. Free radicals are naturally produced during the course of everyday metabolism and, in excess, can harm DNA and other molecules by causing oxidative stress.

This 1956 paper by Dr. Harman helped popularize a belief system that aging could be mitigated or even conquered by addressing the free radical problem. While extremely appealing, this theory turned out to be way too simple.[2] Not only are free radicals essential for normal processes within our bodies, but boosting antioxidant defenses failed to give the kind of results in animal models that were expected if this theory were true.

This doesn't mean that oxidative stress doesn't have a role to play in the aging process. It absolutely does and can lead to damaged DNA and cause cells to enter a state of senescence. It does mean, however, that aging itself is profoundly more complicated and multifactorial.

Well-deserved optimism or irrational "hopium"?

I use this example because the longevity field is especially prone to hype and rallying behind an overly naive, sanguine explanation for what causes aging. This doesn't mean that the scientific progress isn't remarkable or that there isn't reason to be optimistic about the future, but it does mean that the longevity space has a tendency to enthusiastically barrel ahead without waiting for the evidence.

Indicative of this, results of a survey given to 103 longevity researchers suggest that the field is very much in a state of techno-optimism.[3] In this survey, participants were asked to choose, on a five-point scale, how much they agreed with the following statement: "The average lifespan in developed countries will be increased by >10 years in the next 20 years." To my surprise, a significant majority of aging experts indicated agreement with this projection.

A monumental challenge

While not totally impossible, massive obstacles would have to be overcome to extend average lifespan by more than 10 years in the next two decades. To give you a sense of just how epic this would be, a prior analysis showed that completely preventing every single cancer death in the United States would only increase life expectancy by around three years.[4] Likewise, most of the gains in life expectancy since 1900 in the United States are due to an improved ability to prevent and treat infectious and contagious diseases. Once you control for the eight most infectious and contagious diseases, the overall improvement in lifespan since 1900 shrinks considerably.[5]

At this point, the average life expectancy in developed countries around the world is close to 80

years.[6] What would it take to increase this by more than a decade within the next 20 years? This is a non-trivial question and I suspect that the majority of survey respondents weren't thinking about what would realistically be needed to pull this off.

There are a few obvious problems to keep in mind. First of all, lifespan studies in laboratory mice or primates take years to complete, and not every lab can spare the time and resources to appropriately complete these studies. Beyond this, the vast majority of mouse studies fail to translate to humans[7] and transition from experimental discovery to clinical translation takes about 10-15 years.[8] Furthermore, most mouse lifespan studies extend lifespan too modestly to realistically result in a 10+ year increase in average lifespan.

Assuming a typical lifespan of around 80 years, a therapy would have to extend lifespan by over 12.5% to get average lifespan to beyond 90 years. If you take a look at all of the successful studies done by the National Institute on Aging's Interventions Testing Program, the vast majority of supplements and drugs found to extend lifespan don't hit this 12.5% threshold.[9] Across male and female mice, the only compounds that extend average lifespan by at least 12.5% are rapamycin alone, acarbose alone, a combination of rapamycin and acarbose, or a combination of rapamycin and metformin.[9]
Even if one of these worked in humans, it's important to note that a direct translation of effect size is highly unlikely.[10,11]

To see a radical longevity payoff with a traditional translational approach, humanity would have to start running huge numbers of extraordinarily expensive and well-powered lifespan studies testing different therapeutics in the very near future. If you're interested in digging deeper, I recently published a more detailed, technical account of my skepticism in the scientific journal *Biogerontology*.[9]

IMAGE SOURCE: MAJID RANGRAZ VIA UNSPLASH

Arguing on behalf of the techno-optimist

Of course, I would be delighted to be proven wrong and for average lifespan to continuously jump upwards in the near future. I'd be even happier if these lifespan gains were accompanied by improvements in healthspan. Perhaps rapid advances in artificial intelligence will indeed upend traditional drug development and massively accelerate the processes of drug discovery and translation.[12] It's also possible that major advances in our ability to understand and measure biological aging will occur,[13] allowing extremely costly, time-consuming studies to be replaced with much more affordable, shorter trials using biomarkers that are surrogates for future longevity.

Final thoughts

Fundamentally, I believe that most of the surveyed longevity experts answered the way they did because they're extremely optimistic about the future of aging science and impressed by how much the field has advanced in recent decades. I'm impressed too, but it's important to embrace the reality of how complicated aging is and how difficult it is to meaningfully intervene beyond adopting a holistically healthy lifestyle. Despite all of this, I have no doubt that the longevity field will continue to move forward and make substantial strides. The details and timing of those strides, however, remain to be determined.

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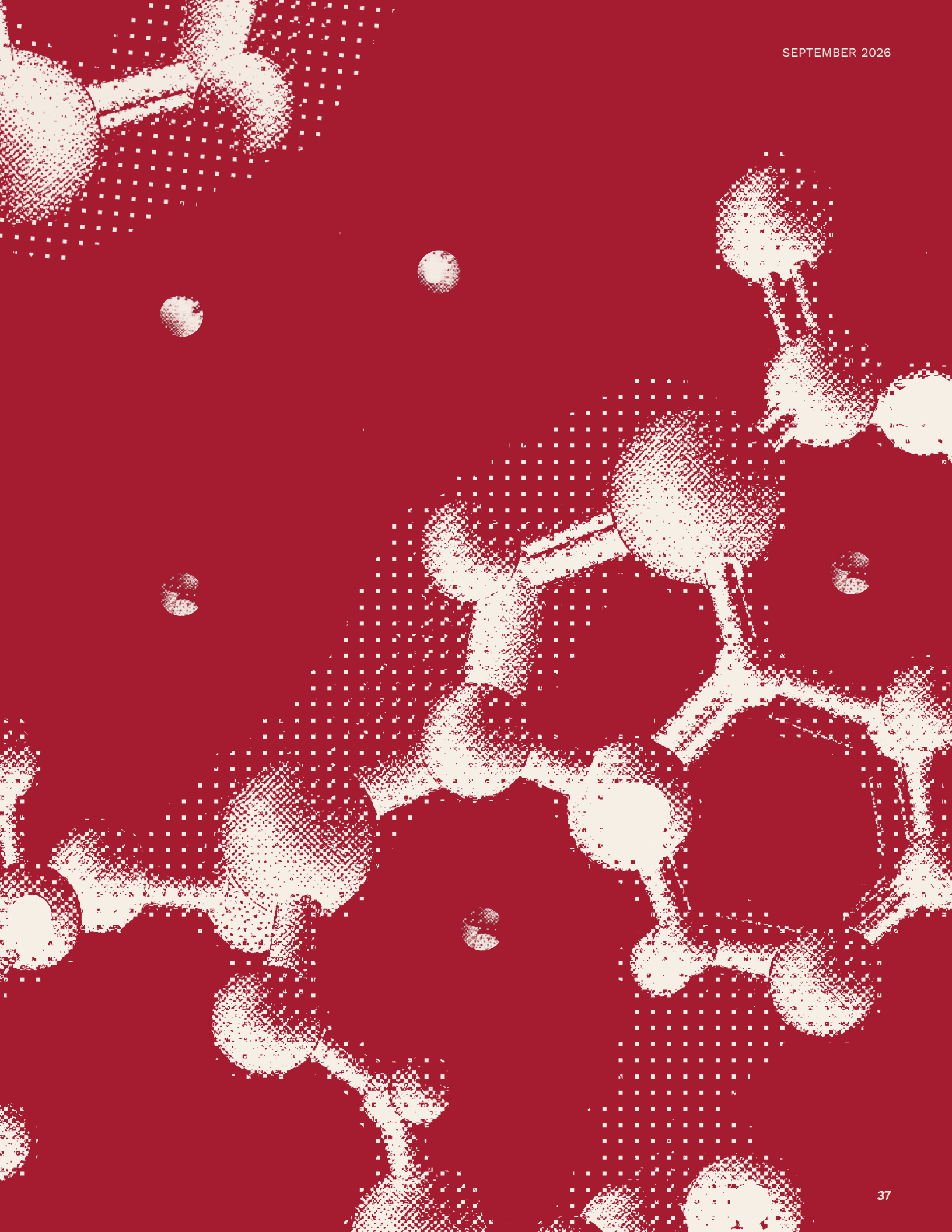
IMAGE SOURCE: AI-GENERATED WITH OPENAI

OPINION

BLOOD NAD^+ LEVELS TELL US LESS THAN MANY PEOPLE THINK

BY DAVID A. SINCLAIR, AO, PHD

IMAGE SOURCE: AI-GENERATED WITH OPENAI



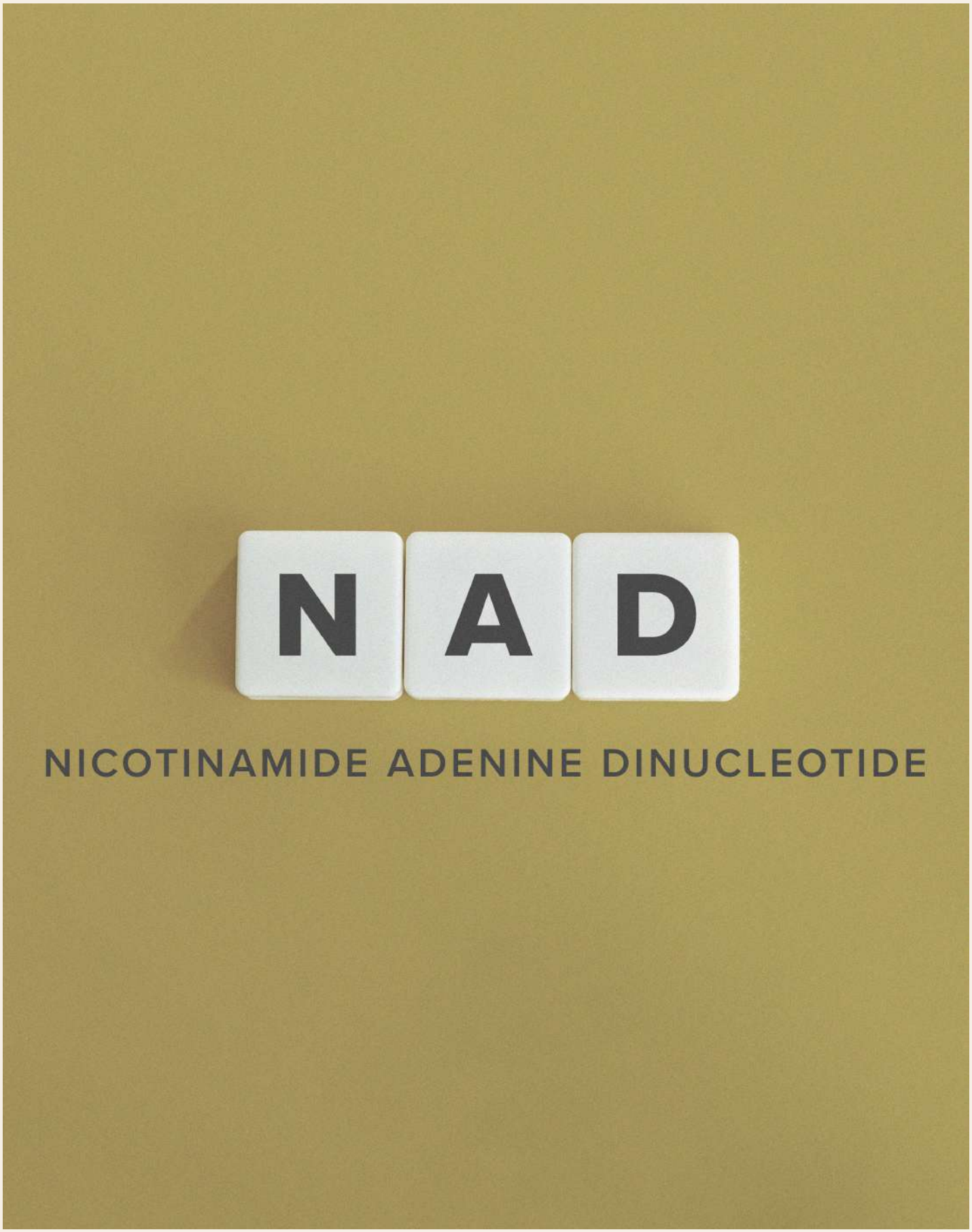


IMAGE SOURCE: PHOTOOPUS VIA ADOBE STOCK

One of the easiest mistakes in science is to confuse a single measurement with the whole reality. We do it all the time. An investor watches a stock price and forgets that the ticker is not the company. A person steps on a scale and begins to believe the number is their health. A physician measures cholesterol, glucose, or blood pressure and gradually starts treating the number rather than the person. The measurement, once a useful clue, slowly becomes a substitute for the living system it was meant to describe. The map begins to replace the country.

Every scientific field eventually confronts this temptation. The numbers become so familiar, so useful, and so precise that scientists begin to forget they are merely shadows cast by a complicated reality. In longevity research, where scientific questions often become proxy battles for much larger disagreements, this mistake was recently made in dramatic fashion.

A paper published in *Nature Metabolism* from the laboratory of Professor Riekelt Houtkooper at the University of Amsterdam, and amplified by a widely read T*he New York Times* article, reported that levels of nicotinamide adenine dinucleotide, better known as NAD^+, remain remarkably stable in human whole blood throughout adulthood.[1]

Reaction to the Houtkooper article was swift. Within hours, social media was filled with confident interpretations of the study. The conclusion was irresistible: if NAD^+ levels in blood do not decline with age, then the entire premise behind the NAD^+ precursors nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) as well as decades of research into NAD^+ biology must have been misguided from the beginning. It was a reminder that conclusions often travel faster than understanding.

Throughout the week, there was a noticeable sense of schadenfreude, the quiet satisfaction some people derive from the misfortunes of others. Since NAD^+ was identified as the fuel for protective sirtuin enzymes in the late 1990s, the field has attracted passionate advocates, determined critics, commercial interests, bold claims, and equally bold dismissals. As often happens in science, a single paper became a stand-in for a much larger debate.

To understand why the recent paper attracted so much attention, it helps to understand what NAD^+ is and why so many people care about it. NAD^+ is a small molecule found in every living cell, where it helps convert food into energy and supports processes ranging from DNA repair and gene regulation to cellular signaling and stress resistance. Because many of the enzymes linked to healthy aging – including the sirtuins, depend on NAD^+ to function, researchers have spent the last two decades exploring whether boosting NAD^+ levels might help aging cells behave more like younger ones. That idea gave rise to NAD^+ precursors such as NR and NMN, molecules that cells can convert into NAD^+ through natural salvage pathways. NR and NMN are classified as "dietary supplements", meaning they can be purchased without a prescription.

What began as a niche area of aging research has since grown into one of the most visible sectors of the longevity movement, spawning a global market worth hundreds of millions of dollars, attracting billions in investment, and turning NAD^+ into one of the most recognizable molecules in modern aging biology. The story of NAD^+ has ultimately morphed into a battle over reputations, careers, and balance sheets.

The problem was not with the Houtkooper study. On the contrary, it answered an important question with impressive rigor. The problem arose when a study about blood NAD^+ was interpreted as a verdict on NAD^+ biology itself.

Professor Houtkooper's study asked a straightforward question: do NAD^+ levels in whole blood decline with age? It is a reasonable question and an important one. But it is not the same as asking whether NAD^+ metabolism changes within aging tissues and whether those changes contribute to the loss of function we call aging. At first glance, these questions appear closely related. In reality, they lead in very different directions.

Which brings us to the question that spread through social media with such enthusiasm: if NAD^+ does not decline with age, why would raising it matter?

The answer is that the value of a biological intervention is determined by whether it improves function, not whether it replaces something that has disappeared. What matters is not simply whether a molecule is present, but whether the pathways that depend upon it are functioning optimally and whether enhancing those pathways improves health.

The Houtkooper study provides strong evidence that whole-blood NAD^+ levels remain relatively stable across the adult lifespan.[1] What it does not demonstrate is that NAD^+ remains stable in every tissue throughout the body. Nor does it tell us whether increasing NAD^+ availability can improve the function of aging tissues. Those are different questions, and they remain very much open.

The distinction matters because blood is not the body. Aging unfolds within neurons, stem cells, muscle fibers, immune cells, and other tissues that gradually lose function over time. The central question is therefore not whether NAD^+ declines in blood, but whether NAD^+ biology changes within the tissues that age.

What makes the current debate particularly interesting is that some of the strongest evidence suggesting that NAD^+ biology is tissue-specific comes from the same group of scientists that reported the stability of blood NAD^+. In 2022, Dr. Georges Janssens and colleagues, including Houtkooper, published a landmark paper in *Nature Aging* examining NAD^+ levels in skeletal muscle from young adults, healthy older adults, physically trained older adults, and functionally impaired older adults.[2] NAD^+ was one of the metabolites most depleted in aging muscle. The lowest levels were found in older adults with physical impairments. Meanwhile, older adults who exercised regularly maintained NAD^+ levels that were remarkably similar to those of much younger individuals. He reported this, to much fanfare, at the Aging Research and Drug Discovery conference in Copenhagen, Denmark in 2021.

"Studies using magnetic resonance spectroscopy have reported age-related declines in brain NAD^+ levels Investigators examining liver tissue have observed lower NAD+ concentrations in older individuals."

Yet the recent study from the Houtkooper laboratory then reported that NAD^+ levels in blood remain stable throughout adulthood.[1] Findings from both papers can be true. Yet somewhere between those two papers an important nuance was lost. The earlier study suggested that NAD^+ biology is tissue-specific and associated with health status in

human aging. The later study demonstrated that blood NAD^+ is not a useful biomarker of aging. Those are not contradictory conclusions.

Studies using magnetic resonance spectroscopy have reported age-related declines in brain NAD^+ levels.[3,4] Investigators examining liver tissue have observed lower NAD^+ concentrations in older individuals.[5] Evidence from other tissues points in the same direction. Human skin samples have likewise shown age-associated changes in NAD^+ metabolism.[6] None of these studies are definitive on their own. Sample sizes are modest and each method has limitations. But together they suggest something important: blood may remain stable while individual tissues follow very different trajectories.

There is an even deeper reason to be cautious when interpreting measurements of NAD^+ levels alone. Much of the current debate treats NAD^+ as though it were water sitting in a reservoir. Researchers lower a bucket into the lake, measure the level, and then argue about whether the lake is rising or falling with age. But biology often cares less about the height of the reservoir than the speed of the current.

More than twenty years ago, my laboratory encountered this distinction while studying aging in yeast. We set out to test how altering NAD^+ metabolism would affect yeast lifespan and if one of the sirtuins, Sir2, was involved. We found that manipulating the NAD^+ salvage pathway dramatically extended lifespan and enhanced Sir2-dependent biology, including epigenomic and genomic stability. Yet despite these profound effects, steady-state NAD^+ levels and NAD^+/NADH ratios remained essentially unchanged.[7] The cells lived longer. The pathway changed. Sir2-dependent processes improved. But the amount of NAD^+ sitting in the cell at a single moment barely moved.

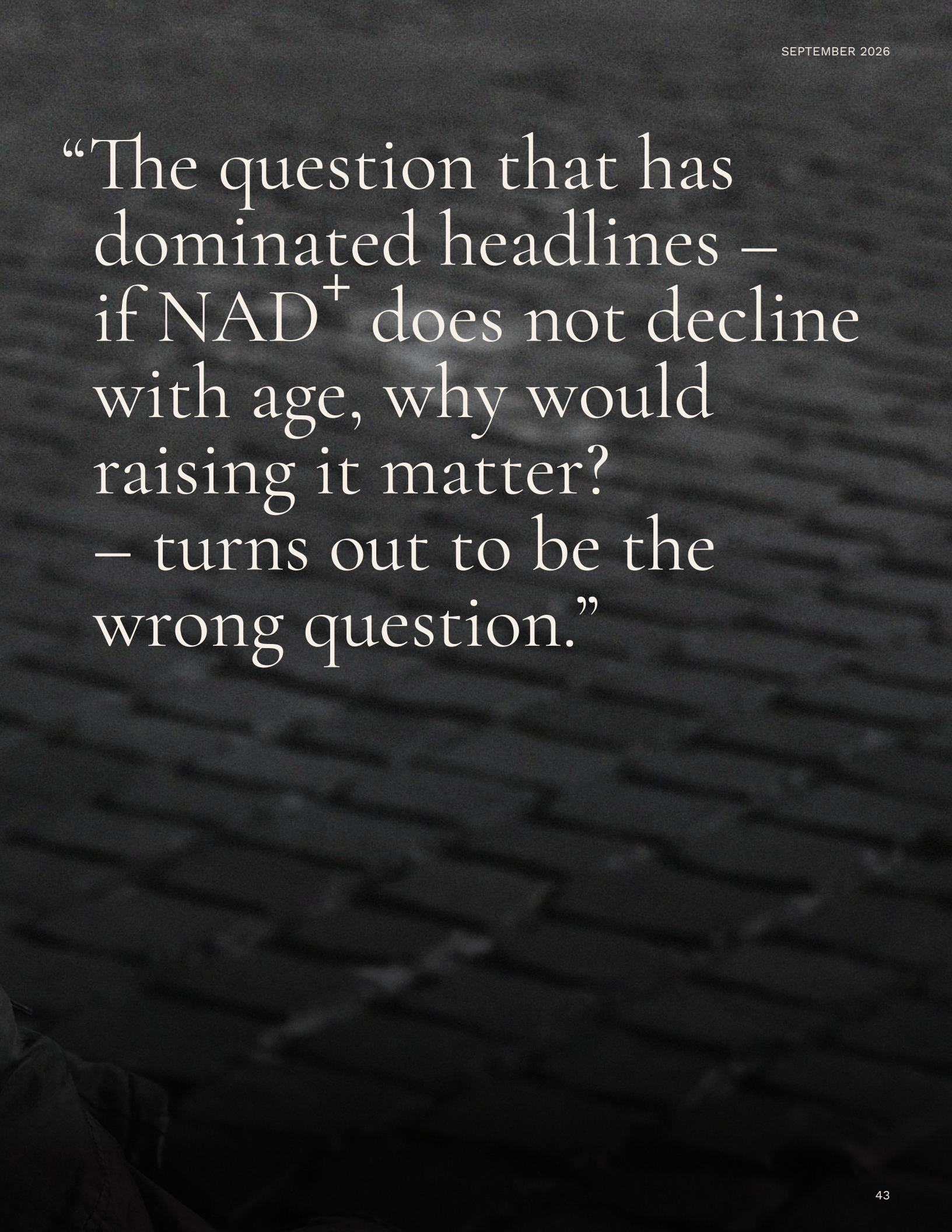
At first this seemed paradoxical. How could a pathway become more powerful if the amount of its key molecule remained the same? The answer was that we had been looking at a photograph when we should have been watching a movie. Cells do not simply store NAD^+ like coins in a vault. They synthesize it, recycle it, consume it, and regenerate it constantly. In a subsequent Nature paper, we showed that calorie restriction and stress induce the expression of PNC1, an enzyme in the yeast NAD^+ salvage pathway that helps govern lifespan extension, an equivalent of the NAMPT enzyme in humans.[8] PNC1 acted like the opening of a floodgate. The important change was not necessarily a larger pool of NAD^+ sitting inside the cell, but greater movement through the salvage pathway and reduced accumulation of nicotinamide, a product that inhibits Sir2 activity.

Biochemists call this metabolic flux. It is one of the most important and least discussed ideas in this debate. Flux is hard to measure, which is why it is often ignored. Concentration is easier. You can measure how much NAD^+ is present in blood and draw a graph.

Measuring how rapidly NAD^+ is being produced, consumed, recycled, compartmentalized, and made available to enzymes in specific tissues is much harder. But difficulty does not make the question less important. If anything, biology has a habit of hiding its most important secrets in the places that are hardest to see.

We learned this lesson years ago when we began studying how cells respond to stress. In 2007, we discovered that NAD^+ levels inside mitochondria-the tiny power plants that generate most of a cell's energy-could determine whether a cell survived or died, even when total cellular NAD^+ levels appeared unchanged.[9] The critical variable was not how much NAD^+ existed in the cell as a whole. It was where the NAD^+ was. A cell could appear well supplied on paper while a compartment essential for survival was running short.

IMAGE SOURCE: JONAS VANDERMEIREN VIA UNSPLASH



"The question that has dominated headlines – if NAD^+ does not decline with age, why would raising it matter? – turns out to be the wrong question."

This observation led us to propose what we called the "mitochondrial oasis" concept: the idea that understanding NAD^+ biology requires understanding where NAD^+ resides and where it is needed. Like an oasis in a desert, a small pool in the right place can matter more than a vast reservoir somewhere else.

The implication was both simple and profound. You could grind up a cell, measure its total NAD^+ content with exquisite precision, and still miss the biology that mattered most.

The recent Amsterdam study measured abundance, not flux or compartmentalization.[I] That is not a flaw; it is simply what the study was designed to do. But it means the study cannot tell us whether NAD^+ turnover, recycling, intracellular distribution, or availability to key enzymes changes with age. Those are not small details. They may be the very details that determine whether a cell continues to function or begins to fail.

Ultimately, the most important question is not concentration or even flux. The most important question is function. Can manipulating NAD^+ metabolism improve human physiology? This is where the public debate often becomes too crude. One side treats NAD^+ precursors as if they were proven longevity drugs. The other treats a stable blood measurement as if it were evidence that the entire field is baseless.

In recent years, some of the most rigorous human studies addressing function have been conducted by Dr. Shalender Bhasin and colleagues using MIB-626, a pharmaceutical-grade microcrystalline tablet of beta-nicotinamide mononucleotide (beta-NMN).[10,11] Here, I wish to note that I am a founder and co-owner of MetroBiotech International, the Boston-based company that sponsored this research but had no role in the actual clinical trials beyond data analysis.

The 2023 Bhasin studies[10,11] had already hinted that blood NAD^+ may not be a simple aging biomarker. In carefully controlled trials of middle-aged and older adults, baseline and treatment-related changes in circulating NAD^+ were not strongly tied to age, though the studies were small and not designed to map NAD^+ across the lifespan.

In their first double-blind, placebo-controlled study of middle-aged and older adults, MIB-626 substantially increased circulating NAD^+ and its metabolome.[10] Then, in a randomized trial of overweight or obese adults aged forty-five years and older, two grams of MIB-626 a day safely increased circulating NAD^+ levels and significantly reduced body weight, diastolic blood pressure, total cholesterol, LDL cholesterol, and non-HDL cholesterol compared with placebo over 28 days.[11] The study did not show significant changes in insulin sensitivity, or liver and abdominal fat, and it was not designed to determine whether beta-NMN extends lifespan. But it did show that manipulating NAD^+ metabolism in humans can produce measurable physiological effects.

That fact matters. The Amsterdam blood study asks one question: does whole-blood NAD^+ decline with age? The 2023 clinical studies ask another: does increasing NAD^+ availability influence human biology? Neither question answers the other. A stable blood level does not prove that raising NAD^+ is useless, just as the ability to raise NAD^+ does not prove MIB-626 will work. The reasonable conclusion is more careful and more interesting: NAD^+ biology is real, tissue context matters, and clinical outcomes must be tested directly.

By this point, the flaw in the argument should be apparent. The Amsterdam study measured NAD^+ levels in whole blood and found that they remain remarkably stable across adulthood.[I] It did not measure NAD^+ in every tissue. It did not measure NAD^+ flux. It did not measure the availability of NAD^+ to specific enzymes. And it did not test

whether increasing NAD^+ improves physiological function. Yet some commentators boldly leapt from "blood NAD^+ does not decline with age" to "NAD^+ is therefore irrelevant to aging."

This is a category error: mistaking the map for the country, the road for the city, the value of a single metabolite for complex biology.

The question that has dominated headlines – if NAD^+ does not decline with age, why would raising it matter? – turns out to be the wrong question. It assumes that the value of a biological pathway depends on whether its components disappear with age. We do not judge the importance of exercise by asking whether people are born unable to walk. We judge interventions by whether they improve function.

The recent findings have not closed the book on NAD^+ biology and the utility of NAD^+ precursors. They have reminded us that the story is more complicated than the headline, and in biology, the most interesting stories usually are.

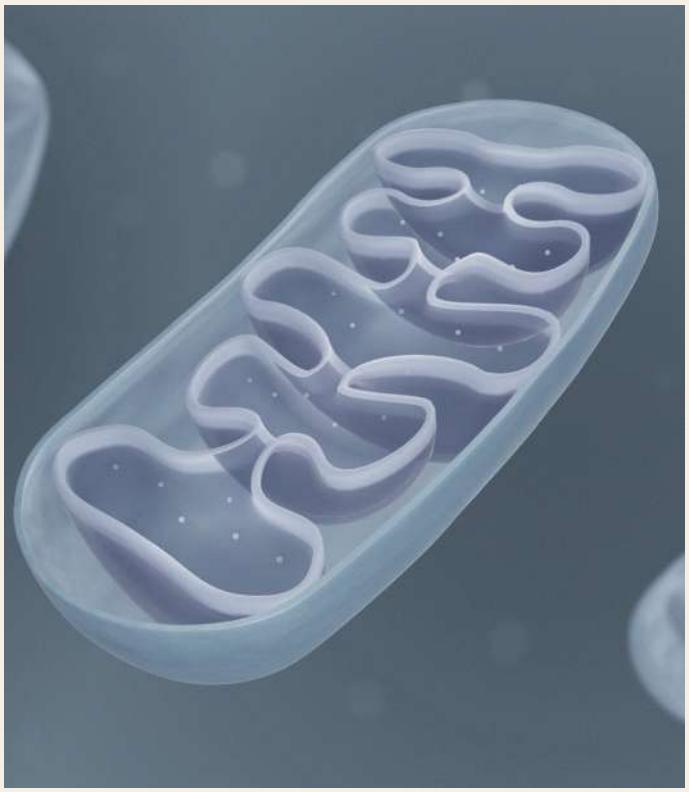


IMAGE SOURCE: ARTUR VIA ADOBE STOCK

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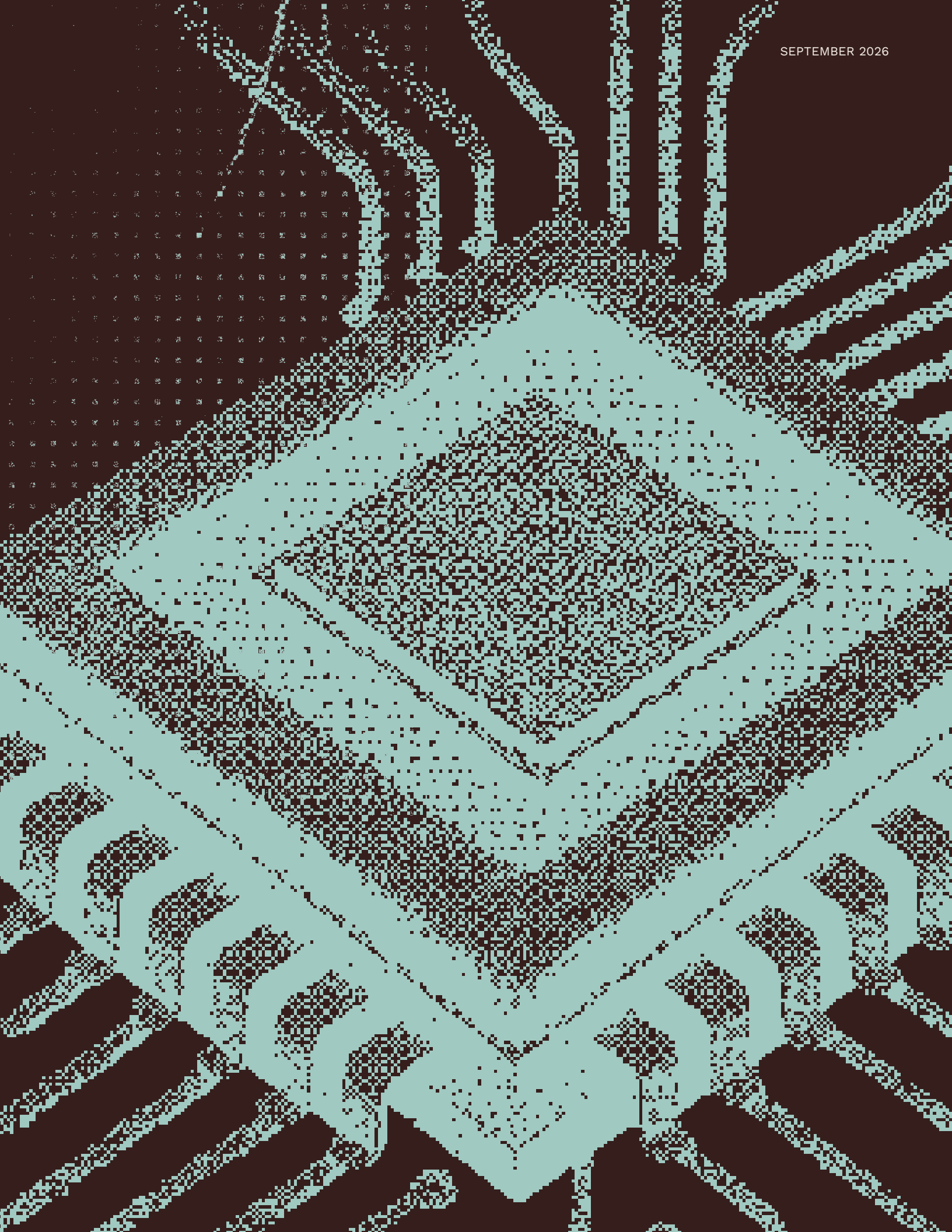
HUMAN ON A CHIP

BY DAVID A. SINCLAIR, AO, PHD

IMAGE SOURCE: DAVID A. SINCLAIR


SEPTEMBER 2026

For over a century, drug development has faced a persistent problem: spectacular results in mice, slow progress and disappointing results in humans. That is why one of the most exciting papers to emerge recently is not another mouse study or clinical trial.

Published in *Nature Biomedical Engineering*,[I] Professor Andreas Stahl, the Ruth Okey Chair in Metabolic Biology and Nutrition and his postdoc Dr. Lin Qi built a human aging-on-a-chip model from human white adipose tissue and liver, then exposed it to serum from younger and older donors. In just four days, the system induced multiple hallmarks of aging that normally unfold over decades, including senescence, oxidative DNA damage, inflammatory signaling, insulin resistance, and metabolic dysfunction.

The researchers grew these organs from induced-pluripotent stem cells (iPSCs), which allows them to be mass produced and tested against thousands of molecules to find those that reverse aging – in human tissues.

What is particularly impressive is that the chip did more than mimic aging. It captured the conversation between tissues. Aged fat transmitted pro-aging signals to the liver, driving inflammation, senescence, and insulin resistance. That matters because aging is not a single-organ event. It is a network failure.

In an exclusive interview with *Lifespan*, Dr. Stahl said "my biggest surprise was that we were able to establish hallmarks of cellular aging using human iPSCs. iPSC-derived cell types are often considered to be immature or neonate-like but the human serum could quickly establish aging phenotypes. Indeed, both cells treated with young or old serum were quite distinct from cells without any human serum and we are following up on the idea that human serum could drive maturation."

When asked about the most exciting moment, Dr. Stahl said "I remember how surprised and excited I was when Dr. Qi showed me the rows of blue and white wells within the adipocyte chip stained for induction of senescence. The effects of serum from old vs. young donors were visible to the naked eye even in this small microfluidic device. With such a robust effect I knew that we were on the right track."

For the first time, Drs. Stahl and Qi have made a human-relevant system that lets them watch that network break down on a practical timescale. It's easy to imagine follow-on systems that link brain, pancreas, thymus, muscle, and blood in more complex 'multi-organ' chips

When asked how he came up with the idea to test serum, Dr. Stahl said, "I had read the seminal papers about effects of heterochronic serum exchange in symbiotic mouse models, but our organ-on-a-chip research was mostly focused on obesity related diseases such as diabetes and fatty liver disease."

"During a brainstorming session with some of my colleagues from UC Berkeley's QB3 initiative, Dr. Irina Conboy, a co-corresponding author on our paper, suggested we should try the heterochronic serum idea with our stem cell-based adipocyte and hepatocyte microphysiological systems. I admit that I was initially skeptical but Irina was quite convincing and introducing a small amount of human serum into the circulation of our liver and fat chips was easily done from a technical standpoint."

The real headline, here, is speed. Dr. Stahl's new platform lets the team test rejuvenation strategies quickly. The strongest effects were seen when old serum was diluted and combined with candidate longevity drugs. Oxytocin, the feel-good hormone, stood out as the most effective single agent for

overriding old-serum effects, reducing senescence and inflammation while improving glucose and lipid metabolism.

This is not proof we can reverse human aging tomorrow. It is, however, an important step: a new system for testing intervention in humans faster than we can in mice.

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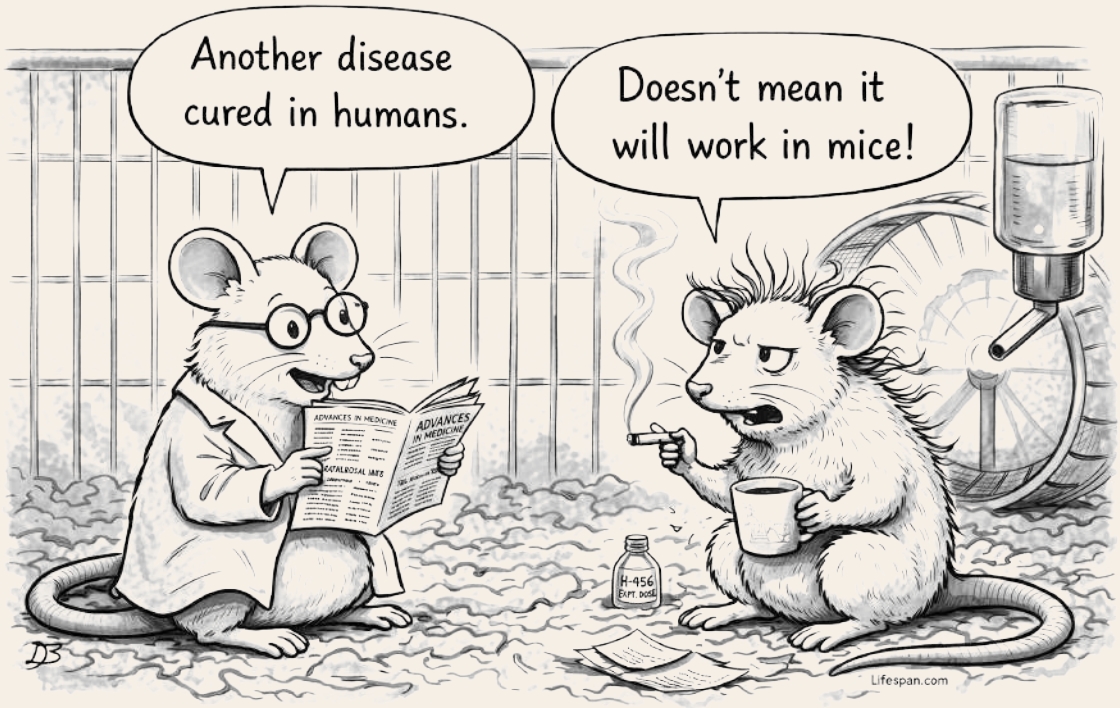
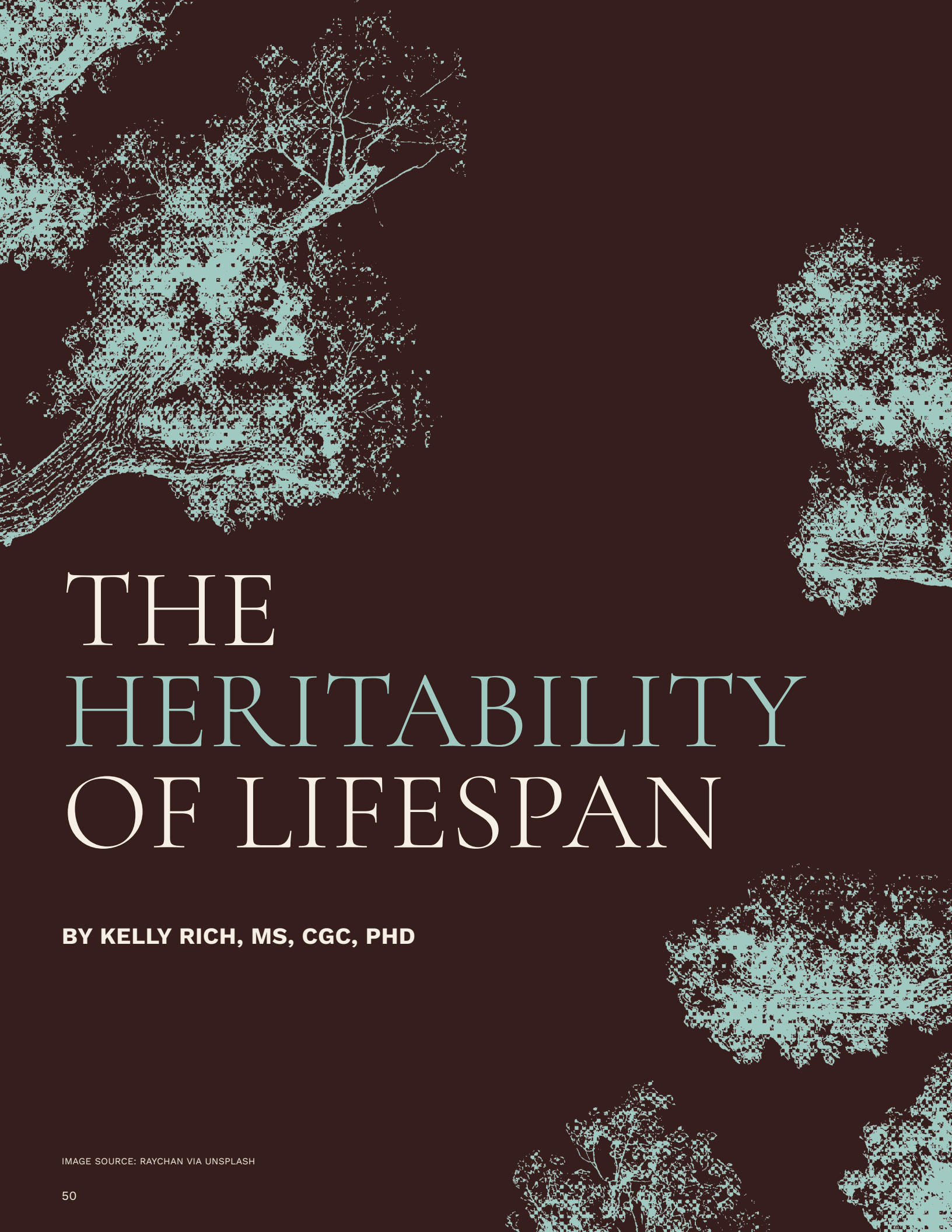


IMAGE SOURCE: DAVID A. SINCLAIR, AO, PHD VIA AI



THE HERITABILITY OF LIFESPAN

BY KELLY RICH, MS, CGC, PHD

IMAGE SOURCE: RAYCHAN VIA UNSPLASH

“When it comes to lifespan, how much is in our own hands?”

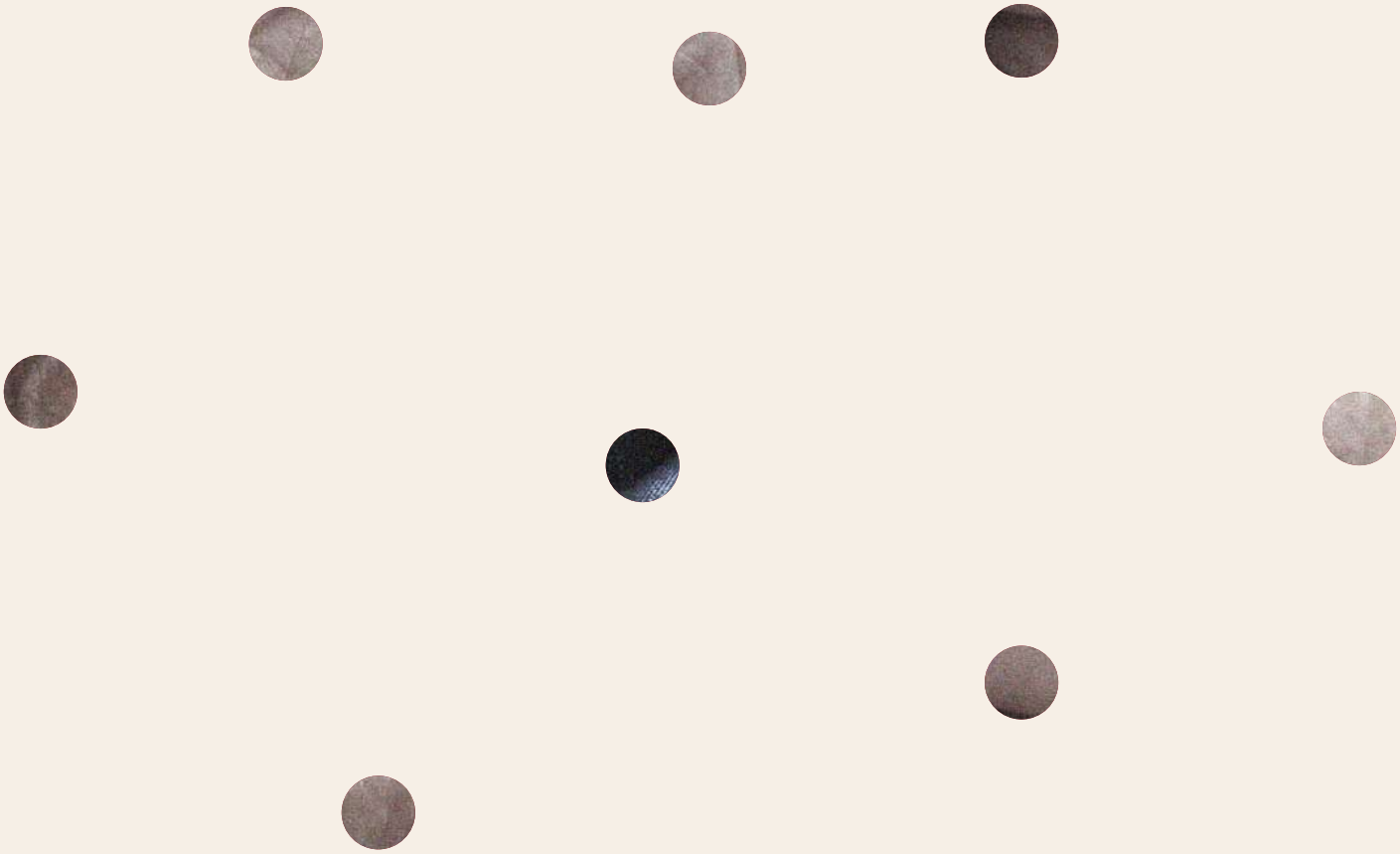
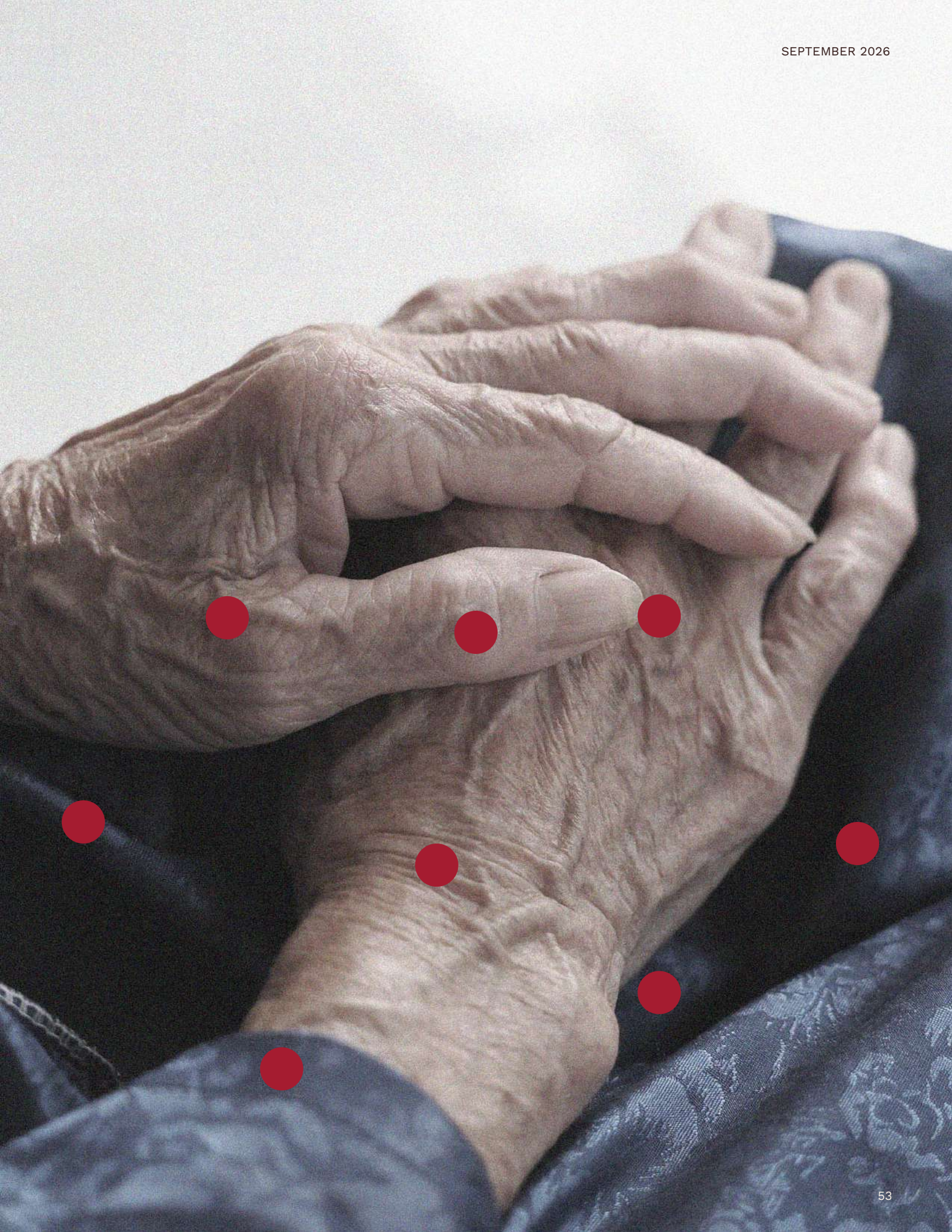


IMAGE SOURCE: DANIE FRANCO VIA UNSPLASH



There's a familiar character in modern medicine: the perfect patient. The person who does everything "right." They eat sensibly, exercise regularly, avoid obvious vices, keep up with screenings, floss every day, and keep a close social circle. Public health campaigns, wellness apps, and risk calculators implicitly promise that if you check the boxes, you can (more or less) bargain with fate. The perfect patient is the kind of person guidelines are written for, and the rest of us are graded against.

And yet most of us can think of people whose lives flat-out defy the script. There's the marathon runner with a sudden heart attack, or the never-smoker with lung cancer. On the other hand, we all know a *how-are-they-still-alive?* character who breaks every rule and somehow reaches a ripe old age. These outliers sit uneasily beside the idea that behavior is everything. They raise a question that is both scientific and painfully personal: when it comes to lifespan, how much is in our own hands?

Part of why this question interests me so much is my day job. I come to this conversation as someone whose career has been built on competing narratives.

I was originally trained as a genetic counselor, a clinician tasked with assessing genetic risk of disease across individuals and families. Anyone who works in clinical genetics is acutely aware that a single mutation can feel like a verdict.

These days, my career has shifted more from genetics to epigenetics, studying the molecular tags on our DNA that influence which genes get switched on. Your epigenome is shaped by many of the things the perfect patient tries to optimize (diet, sleep, stress, exercise), which can, in principle, rewrite some of the risk written into our genomes. Living at the intersection of fixed DNA and flexible biology makes it hard for me to see lifespan as either pure destiny or pure choice.

The perfect patient raises a more honest question. Not, "is it all genes?" or "is it all lifestyle?", because those simple yes-or-no questions are from a time before we could truly measure how genes and the environment work together. Today, the real question is: What aspects of our lifespan can we actually control, and where, no matter how hard we try, do we have to accept that there are things beyond our ability to fix?

What heritability is (and is not)

When people argue about control and lifespan, they often reach for a number: "X% of how long you live is genetic." It sounds satisfying and precise, as if you could divide your years into a DNA slice and a personal-choice slice. That number comes from something called *heritability*. But heritability is not a verdict on your future but rather a population statistic about why people differ from one another. To understand what any "50% genetic" claim really says about control, we must unpack what that word means.

You can see this most clearly at the extremes. Some highly-penetrant monogenetic conditions really are almost all genetics. If you inherit two mutated copies of the *CFTR* gene, you have cystic fibrosis. If you inherit a Huntington's mutation, the disease will almost certainly show up if you live long enough. In most cases, those mutations shorten lifespan. Their "heritability" is effectively 100% because, in families that carry them, who gets sick and who doesn't is almost entirely explained by who inherited the mutation.

On the flip side, some traits have essentially 0% heritability, like what language you speak, the food you

eat and what skills you learn. That part is entirely about the environment you grow up in.

Most traits, however, fall somewhere in between. Take height, for example. In many wealthy countries, height has high heritability, around 70-80%.[1] That does not mean your height is 80% genes and 20% breakfast cereal. It means that, among people who are all getting broadly similar food and healthcare, most of the *variation* in how tall they end up can be traced back to their genes. We know the environment still matters because whole populations grew several inches taller over the 20th century as nutrition and public health improved, despite height being "highly heritable".

The math of lifespan

So, what do the heritability numbers look like for lifespan? Different studies have taken a look at this, with different answers.

The classic tools are twin and family studies. Identical twins share nearly all their DNA, while fraternal twins and regular siblings share about half. If genes matter, identical twins should have more similar lifespans than fraternal twins raised in the same world. That extra similarity is what researchers attribute to genetics.

Large twin cohorts usually land in the same range: genetics seems to explain about 15-30% of the differences in how long people live, with hints that genes matter more for those who make it to very old ages.[2,3] Family trees of centenarians tell a similar story: long-lived people often have long-lived siblings, suggesting there really is some inherited advantage for surviving into late life.[4]

Other studies have tried to correct for the fact that families share more than just DNA. People often pick partners who are like them in education, income, and health habits. They share homes, neighborhoods, and cultures. When large genealogy studies try to factor in this assortative mating and shared environment – by looking at in-laws and distant relatives as well as blood relatives – the estimated genetic share for lifespan can drop below 10%.[5]

Another approach is to use genome-wide association studies (GWAS), an approach which evaluates the genetics of (usually) thousands of people. To use GWAS to study longevity, we'd need to look for specific genetic changes that are more common in long-lived people. GWAS studies have turned up a small number of "longevity-linked" spots, including genes involved in cholesterol, immunity, and brain aging.[6,7] But when you add up the effects, all those common variants still explain only a small slice of the overall variation in how long people live (often less than 10%) and "polygenic scores" built from them barely improve on simple clinical risk factors like smoking or blood pressure.[8]

IMAGE SOURCE: EFSTOCK VIA ADOBE STOCK

A new angle

In January 2026, a study published in the journal Science made headlines. Instead of looking at observed *lifespan*, which is the age someone was when they died for any reason, researchers estimated intrinsic lifespan by statistically removing deaths that look clearly external: accidents, infections, war, poor sanitation, and so on. It's a simple twist on an old question.

When you set aside external deaths, most of what was left were chronic diseases that showed up late in life. Under those conditions, heritability estimates jumped above 50%.[9]

That number is intriguing but controversial. It depends on where you draw the line between "external" and "internal" causes. Is dying of flu purely external if your immune genes matter? Importantly, the study hasn't yet been replicated or tested outside relatively wealthy, modern populations. But it certainly has stirred things up. And if you're curious about how far we can realistically push our lifespan in practice, my colleague Adiv Johnson, PhD digs into this more in his recent article "*How Long Can We Actually Expect to Live in The Coming Years?*", and why adding even 10 extra years to average lifespan in developed countries would be an enormous challenge.

For most people, a heritability estimate above 50% won't change anything about their healthcare. But those of us who work in genetics can see where the logic might go next: more genetic tests that claim to predict how long you'll live, IVF clinics hinting they can select "long-life" embryos, drugs and gene-editing programs pitched at "longevity genes," and, in the background, a potential shift of attention away from the basics that still matter most: clean air, safe housing, vaccines, primary care, and blood-pressure control.

"When you set aside external deaths, most of what was left were latelife chronic diseases. Under those conditions, heritability estimates jumped above 50%"

Stepping back, the overall picture is surprisingly consistent. When you look at all deaths together, including things like car crashes, infections, violence, pollution, and inequality, genes seem to play a modest role compared to environment and behavior. But if you zoom in on relatively wealthy countries that have already done the heavy lifting of public health, trauma care, and safer living conditions, the differences that remain in how long people live lean more heavily on genetics.

Choose your parents wisely

So far, we've treated "genes" as the DNA sequence you happen to be born with, and "environment" as everything that happens after. Real biology is, of course, messier. Some of the forces shaping your lifespan started nudging you even before you were born, in the bodies and lives of your parents and grandparents.

This is where developmental programming comes in. Conditions in the womb, including maternal nutrition, blood sugar, stress, and illnesses, can leave lasting marks on how your organs develop

IMAGE SOURCE: JOHN MOESES VIA UNSPLASH

and how your metabolism is set, which is heavily influenced by the epigenome, the software of cells. Individuals who experienced famine in utero or early childhood, including from the Dutch "Hunger Winter" of 1944-45, grow up with higher risks of high blood pressure, Type 2 diabetes, and heart disease.[10,11] Those early signals seem to tweak epigenetic marks and hormone systems in ways that echo across decades.

Then there's the germ cells themselves, the eggs and sperm. Older paternal age increases the number of new mutations children inherit and may influence some later-life disease risks.[12] These effects blur clean categories. Epigenetic marks in sperm and eggs are shaped by environment, yet they can be passed on, looking a lot like genetics from the child's point of view.

For the perfect patient, this is both unfair and strangely freeing. They didn't choose their parents' diets, traumas, or ages, yet this biology helped shape the first chapter of their health story. What they can control, however, is what they pass on. Just as their parents' world influenced their risks, their choices can influence the risks for the next generation. Control doesn't end with their own lifespan.

What's really in your hands

When you look at classic long-term studies, the largest and clearest gaps in lifespan still come from very boring things. A pack-a-day smoker versus a lifelong non-smoker can differ in lifespan by up to 7-10 years, and even more years of disability. People who get their blood pressure under control in midlife have much lower risks of stroke and dementia later. Muscle strength in your 50s and 60s is one of the strongest predictors of whether you'll live independently in your 80s. None of these differences show up because someone had a slightly better longevity polygenic score. They show up because of behavior, treatment, and context.

The same story is told at the molecular level. Epigenetic aging clocks, the tools that read chemical tags on DNA to estimate biological age, change in response to ordinary interventions. Quitting smoking, losing weight, improving blood pressure, exercising more, and eating a reasonably healthy diet are all associated with slower epigenetic aging,[13] and in one small study, a clock ticking backward by two years over just eight weeks.[14]

For the perfect patient, this can feel unsatisfying. There's no gene edit that buys you 40 extra years, no test that guarantees you'll beat the average. At least, not yet. What the evidence does say is less cinematic and more practical: genetics sets a range, but within that range, the basics move the needle by years, not days. The levers aren't as glamorous as a "longevity gene," but they are where most of the control exists.

Rethinking control

Heritability numbers don't translate into a clean predictor of fate versus free will. They tell us how much of the differences between people in a particular time and place are attributable to their DNA. Change the time and place, the infections, the accidents, the food, the inequality, and that percentage moves.

For our perfect patient, that means two things can be true at once. First, there are hard limits: no amount of kale or improvement in VO_2 max can completely erase a pathogenic BRCA mutation or the bad luck of being born into pollution or poverty. Second, within those limits, context and behavior is still able to have meaningful impacts.

This is done through things like not smoking, blood-pressure control, physical activity, and all the advantages of safety, education, and high-quality medical access.

Families with mutations that cause disease and shorten lifespan exist alongside datasets showing that simple changes in behavior and treatment can still shift risk in measurable ways. High-impact genes and modifiable factors are both real; neither cancels the other.

In other words, control operates on multiple levels at once. It includes the choices we make, the conditions our parents and grandparents experienced before we were born, and the public policies that decide who even has a shot at being a "perfect patient."

Longevity science is giving us flashier tools, such as gene editing and epigenetic reprogramming, but none of them replace the basic truth that much of our lifespan still depends on how we live. The real question isn't whether we can out-smart our genes, but how many healthy years we can gain and who gets to enjoy those years.

IMAGE SOURCE: VIKTOR VIA ADOBE STOCK, AI-GENERATED

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DOES RAPAMYCIN BLOCK THE BENEFITS OF EXERCISE?

IMAGE SOURCE: STEPHANIE MORCINEK VIA UNSPLASH

BY ADIV JOHNSON, PHD


SEPTEMBER 2026

RAPA NUI (EASTER ISLAND)
IMAGE SOURCE: STEPHANIE MORCINEK VIA UNSPLASH

Many, many miles west of South America lies a small, triangle-shaped island housing hundreds of ancient, giant stone statues. The native name for this island is Rapa Nui and, in 1722, explorers from Europe visited it on Easter Sunday. Afterwards, this piece of land came to also be known as Easter Island.

Centuries later, a research expedition originating from Halifax, Canada sailed all the way to this remote island. During their visit, the researchers collected many different kinds of specimens for future research, including a simple jar of dirt that was destined to transform longevity science.

Shortly after the expedition, a PhD and microbial scientist named Suren Sehgal started working with this jar in a Montreal laboratory. Dr. Sehgal discovered something fascinating, which is that the dirt was chock-full of a powerful antifungal agent produced by a type of soil bacteria found in Rapa Nui. Having been the first scientist to discover this fungus-killing compound, Dr. Sehgal decided to name it rapamycin, combining *rapa* from the native name of the island with *mycin*, which itself is derived from the Greek word *mykes* for fungus.

This history is fascinating given that rapamycin is now a darling compound among longevity scientists. This molecule has been shown to extend lifespan in many different model organisms, including yeast,[1] worms,[2] flies,[3] and mice.[4] In rigorous, high-powered studies involving large numbers of mice, rapamycin extends lifespan in both males and females. Across all studies, the estimated lifespan extension can range from 8% to 26% and depends on the dose, when treatment is initiated, and the frequency of treatment.[5] In one study, daily rapamycin starting at nine months of age increased median lifespan by 23% in male mice and 26% in female mice.[6]

The drug itself works by inhibiting mTOR, a master nutrient sensor that detects levels of amino acids. mTOR is a powerful conductor that is constantly coordinating both growth and repair. In response to strength training, mTOR gets revved up and initiates muscle hypertrophy and restoration. During longer stretches without food, mTOR turns on reparative pathways like the cellular recycling process autophagy. One of the reasons rapamycin is so beloved by the longevity research community is that it helped unveil the intricate, evolutionarily conserved relationship between nutrient sensing and lifespan.[7]

Rapamycin is uniquely well-evidenced in model organisms, which is why it's been a frontrunner for potential translation to human aging. Recently, the results of the RAPA-EX-01 study – a double-blind, randomized, placebo-controlled clinical trial which tested the effects of rapamycin on exercise in older adults – were made available. The punchline of the trial, which cost more than $700,000, is disappointing.

Results from the study were first published online in April 2026 in the *Journal of Cachexia, Sarcopenia and Muscle* and were based on pre-clinical data in animal models.[8] Specifically, experimental evidence suggested that taking rapamycin intermittently could enhance the benefits of exercise. Inspired by this animal data, the trial took 40 older, sedentary adults with an average age of 72 years and assigned them to one of two groups for a 13-week intervention: 6 mg of rapamycin once per week and home-based exercise or a placebo pill once per week with home-based exercise. The exercise regimen involved cycling and chair-stands (also known as sit-to-stand) three times each week. The trial's primary outcome was a change in how many chair-stands could be performed within 30 seconds while secondary outcomes included C-reactive protein, epigenetic biomarkers, grip strength, physical and mental component scores, and how much distance can be walked over a period of six minutes.

The results were unsatisfying and, frankly, a little concerning. On average, the placebo control group (people who did not take rapamycin) was able to do more chair-stand reps than the rapamycin group and, in sensitivity analyses, this difference was statistically significant. Grip strength and 6-minute walking distance were also lower in the rapamycin group, though neither of these differences reached statistical significance. Next-generation epigenetic aging clocks – methylation-based biomarkers that are associated with all-cause mortality risk in older adults tracked over time – were unchanged by rapamycin. Signaling a potential safety risk, 36 more adverse events also happened in the rapamycin group (99 events) compared to the placebo group (63 events), including pneumonia. This is worth highlighting as, clinically, rapamycin has been traditionally used as an immune suppressant for organ transplant patients.

While the results of this trial suggest that rapamycin might blunt the benefits of exercise, they don't mean that rapamycin can't offer benefits. It's possible, for example, that the dose was too high and given too frequently. The study itself also didn't enroll very many subjects, which means that its reproducibility is questionable and the findings should be taken with a grain of salt. That all being said, the negative results here are understandably concerning to longevity scientists. If the best-evidenced geroprotective drug fails to translate to our species, it makes scientists less confident about what can bridge the gap between mice and humans when it comes to aging.

It's important to remember that mice are not little people and the vast majority of interventions that work in mice don't work in humans. It's still too early to confidently say what rapamycin can or can't do in our species, but the results of this trial suggest that any possible benefits are unlikely to be exercise-related.

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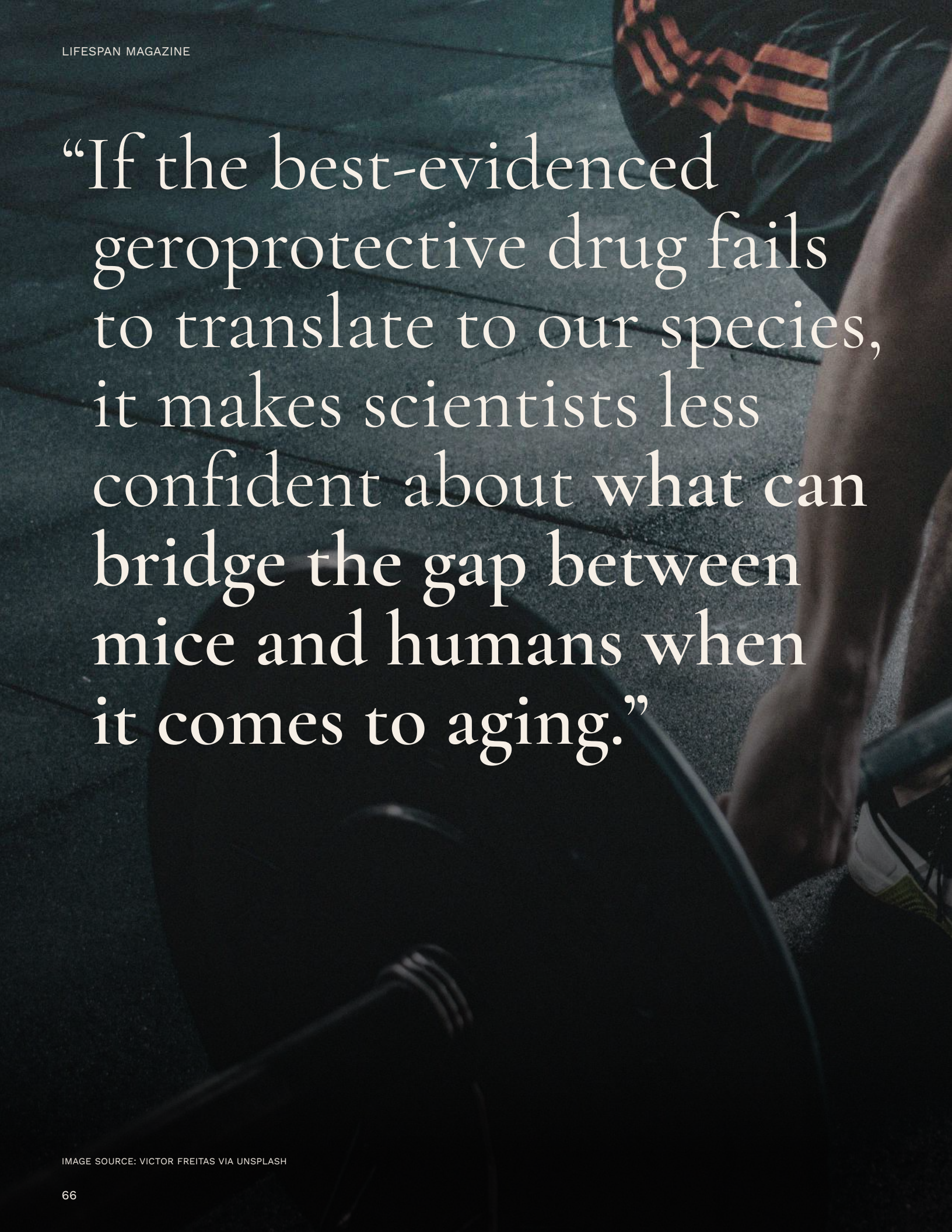
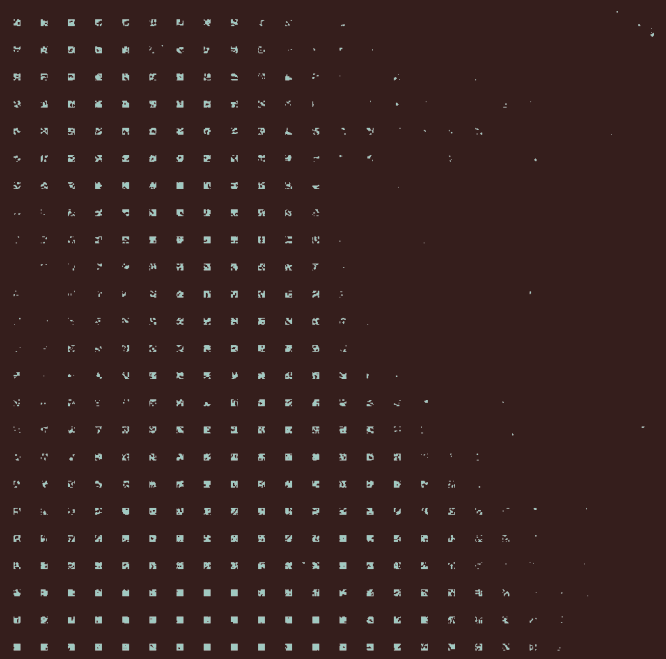


“If the best-evidenced geroprotective drug fails to translate to our species, it makes scientists less confident about what can bridge the gap between mice and humans when it comes to aging.”

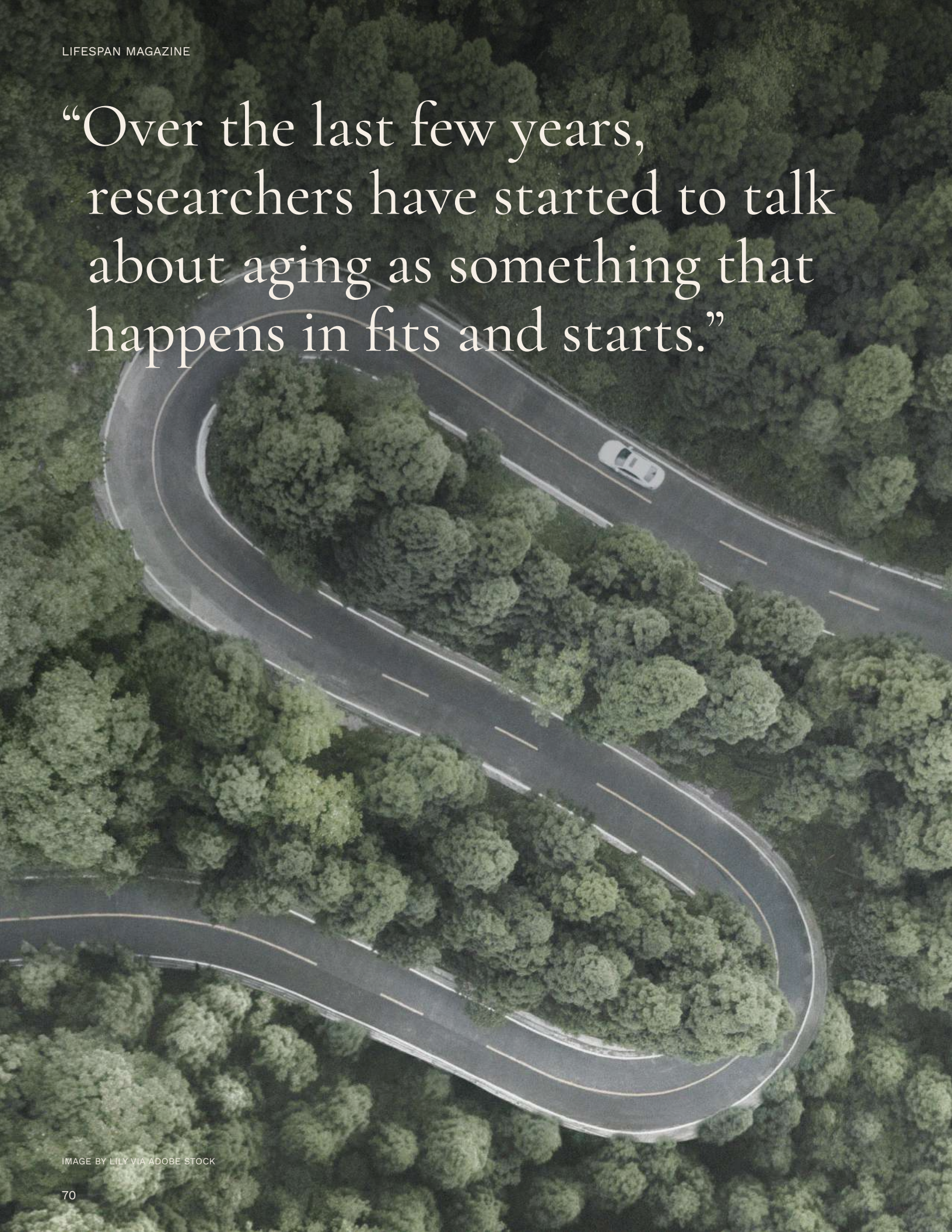
IMAGE SOURCE: VICTOR FREITAS VIA UNSPLASH



THE SURPRISING RHYTHM OF BIOLOGICAL AGING

IMAGE SOURCE: MIDJOURNEY

BY KELLY RICH, MS, CGC, PHD



“Over the last few years, researchers have started to talk about aging as something that happens in fits and starts.”

IMAGE BY LILY VIA ADOBE STOCK

Most health advice imagines aging as a steady slide. Once you hit 40, people joke that you're "over the hill," as if from there it's one long, smooth coast downward. Your biological age and your rate of aging get boiled down to a single line you're supposed to flatten with healthy habits. It's a simple picture, suspiciously so.

If you could watch your body age in time-lapse, it wouldn't look like a slow, even descent. It would look more like a long drive down a mountain road: stretches where you barely touch the gas, stretches where you suddenly hit a steep downhill, and occasional moments where you actually climb a bit before heading down again. Sometimes you're rolling. Sometimes you're braking. Sometimes you're stopped at a light. As it turns out, aging isn't one constant speed.

Over the last few years, researchers have started to talk about aging as something that happens in fits and starts. To see those starts and stops, they've had to measure thousands of molecules at once – markers from blood, the immune system, even the microbiome – and track how they change over time. When you stop forcing the data into a straight line, a different picture appears: biological aging is bumpy, adaptable, and far from linear. That matters, because it changes when your health choices have the most leverage.

The end of the smooth, steady decline

For a long time, our tools to measure biological age were too blunt to pick up much detail. Plot old-school lab values or survival curves against age, and the cleanest line you can draw is a gentle, almost straight slope. The first "biological age" clocks were literally built to match birthdays as closely as possible, which hard-wired a straight line into the math. When scientists re-approached the idea of biological age across the whole lifespan, without insisting it be a straight line, the road suddenly got more interesting.

In a recent study, researchers at Stanford University repeatedly sampled just over a hundred adults in California, aged 25 to 75. At each visit, they measured tens of thousands of molecules: genes, proteins, metabolites, fats, immune markers, and microbes. Then they asked a simple question: how do all these features change as people get older?

Only a small fraction of the molecules drifted up or down in anything like a straight, predictable way. Most stayed fairly flat for years, then lurched into new territory in mid- and late-life. When molecules were grouped by how they changed, two clear spikes in aging emerged – two stretches of downhill road where the car suddenly picked up speed – one centered in the mid-40s, another around 60.[1]

In the first stretch (mid-40s), the molecules that moved together were tied to heart and metabolic health, including things like blood fats, how the body processes alcohol, and signals linked to clogged arteries. In the second (around 60), the pattern shifted toward the immune system, kidney function, and how we handle blood sugar. From the outside, this lines up with what many people notice without ever seeing a scientific figure: blood pressure and cholesterol that were fine suddenly aren't, hangovers last all day, infections hit harder, and recoveries from intense exercise take longer.

Other datasets show similarities in aging waves. One study measuring proteins in human blood saw especially large changes during the fourth, seventh and eighth decades of life, with slower stretches in between.[2] We even see waves of aging in mice.[3] Put together, they sketch out something like a stage map rather than a single clean slope, a winding road

with long flats and sharp descents. The point isn't that everyone hits the same mileage marker at the same birthday. It's that biology has distinct phases where many systems shift together, amounting to periods of big reorganization.

Puberty and menopause as built-in accelerators

Some of the clearest accelerators of age are hard to miss even without blood work: puberty and menopause. As it turns out, these periods are built-in bursts in the aging process – parts of the road where biology presses the gas harder for a while

During adolescence, epigenetic clocks (tools that read chemical tags on DNA to estimate biological age) tick faster in kids who develop earlier and move more quickly through puberty. Earlier breast development, earlier age at first period, and a fast tempo through puberty all track with "older" clock readings, even in teens and young adults.[4,5] Follow kids into their 20s and 30s, and earlier puberty is linked to a more accelerated "cellular aging" profile that blends telomeres, inflammation, and metabolic markers.[6,7]

On the other end of the reproductive span is another moment of acceleration: menopause. Epigenetic-clock analyses show that menopause itself pushes biological age forward in blood.[8] In cohort studies that follow women over time, those moving through the menopausal transition show larger jumps in multi-system biological age than women who remain premenopausal over the same period.[9] Premature or surgically induced menopause makes that downhill stretch even steeper, a pattern seen both in primary data and in systematic reviews of epigenetic age studies.[8,10]

Short shocks and rebounds

Layered on top of these built-in transition periods are events that briefly shove biological age forward and then, at least partly, let it fall back. Researchers at Harvard recently tested biological age in people going through intense but time-limited stressors: major surgery, severe COVID-19, and late pregnancy. The team measured biological age in blood before, during, and after these events using several kinds of measures, including DNA-methylation-based clocks in humans and supporting transcriptomic and metabolomic biomarkers. Biological age estimates rose during the stressful period and then drifted back toward baseline as patients recovered.[11]

Think of this as using your future health on credit. The tasks of mounting an immune response, healing tissue, or maintaining a pregnancy are all biologically expensive. During the event itself (when you are pregnant or actually sick), your biology looks older. When the job is done, some of that apparent aging is reversible. Not perfectly, and not for everyone, but enough that the trajectory bends.

Why biology behaves in waves

Part of the reason we age in fits and starts is biological thresholds. Our bodies constantly run several overlapping repair crews: some fix DNA damage, others mop up reactive molecules, others patrol for infections. For years, these systems can absorb the wear-and-tear and keep damage below a critical level. But once enough small hits add up, or one key control system falters, the balance can flip into a new state: more chronic inflammation, weaker metabolism, stiffer blood vessels. From the outside, that looks like nothing much for a long time

and then, suddenly, blood pressure, cholesterol, and joint pain all seem to change together.

> **"During the event itself (when you are pregnant or actually sick), your biology looks older. When the job is done, some of that apparent aging is reversible."**

Another part is timing differences between organs. The brain, for example, appears to follow an S-shaped curve: relatively stable early on, a midlife phase where networks become more vulnerable to metabolic stress, then a later phase where damage gets sticky and harder to reverse.[12] Bone, muscle, immune cells and reproductive organs each have their own aging trajectories. When several of those trajectories hit their inflection points around the same chronological age, you get a visible surge in aging. Underneath those organ-level patterns sit the usual suspects (or "hallmarks") of aging biology – DNA damage, telomere shortening, mitochondrial dysfunction, senescent cells, altered nutrient sensing – each with its own tempo. They don't all speed up at once, so the combined curve is bumpy by design.

Finally, there's the inherent messiness of complex systems. The networks that keep all these systems in check are full of feedback loops. As those loops weaken, they can transition from stable control into more chaotic dynamics where small early differences snowball into very different aging trajectories. That's one reason two people with similar lab results at 40 can look starkly different at 70. You are not sitting on one smooth conveyor belt. You are traveling on several partly synchronized roads at once.

What this means for you

If aging is stop-and-go, what does that mean for someone trying to stay healthy without making it a second job?

First, some years are simply higher leverage. The basics matter at any age, but they matter extra when biology is naturally picking up speed. For many people, the 40s are one of those stretches. Even if you feel fine, cardiovascular and metabolic pathways are shifting under the hood. That's a good time to take inventory: check blood pressure and cholesterol, look honestly at alcohol and sleep, and build or preserve muscle. Medications like statins or GLP-1s, and habits like strength training, tend to buy more healthy years when started in this window than if you wait until your 60s or 70s. In the 60s and early 70s, the risks shift: infections, drug side effects, and falls are more likely to trigger long recoveries or permanent losses. Matching your efforts to those threats – vaccines to blunt infections, muscle and balance training and bone protection to blunt falls, and hearing and vision care to keep you steady and engaged – can turn what might have been a cliff into a gentler slope.

Short-term shocks are another pivot point. A serious infection, major surgery, complicated pregnancy, or period of intense psychological stress is not just a "bad spell", it's a fork in the road where biological age briefly jumps. The months after are an opportunity to change the slope, not only to "get back to normal." Leaning into rehab, sleep, nutrition, and mental health care in those windows helps determine which future trajectory you return to.

This stop-and-go picture also undercuts the fantasy of perfect behavior. If aging were a smooth slope, every lapse would feel like permanent damage. In reality, biology has slack. Very few of us can sustain flawless habits year after year. What may matter more is showing up for the handful of periods when your systems are actively reshuffling and making those stretches as healthy as possible.

Genes, early adversity, and structural factors like poverty and pollution still set much of the playing field. But nonlinear aging cuts both ways. The same biology that enables sudden declines also allows meaningful slow-downs and partial reversals. Quit smoking, treat hypertension, move more, sleep better, manage weight, and biological clocks often slow – and in some trials, even tick backwards.[13]

The old metaphor of aging was a single hill you roll down. As we now know, the landscape is far more complicated (and far more interesting) than that. You don't choose the whole landscape, but you have more influence than it might seem over how fast you descend, and where you manage to slow down and catch your breath.

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IMAGE SOURCE: ANNIE SPRATT VIA UNSPLASH

THE MOSAIC BODY

BY KELLY RICH, MS, CGC, PHD

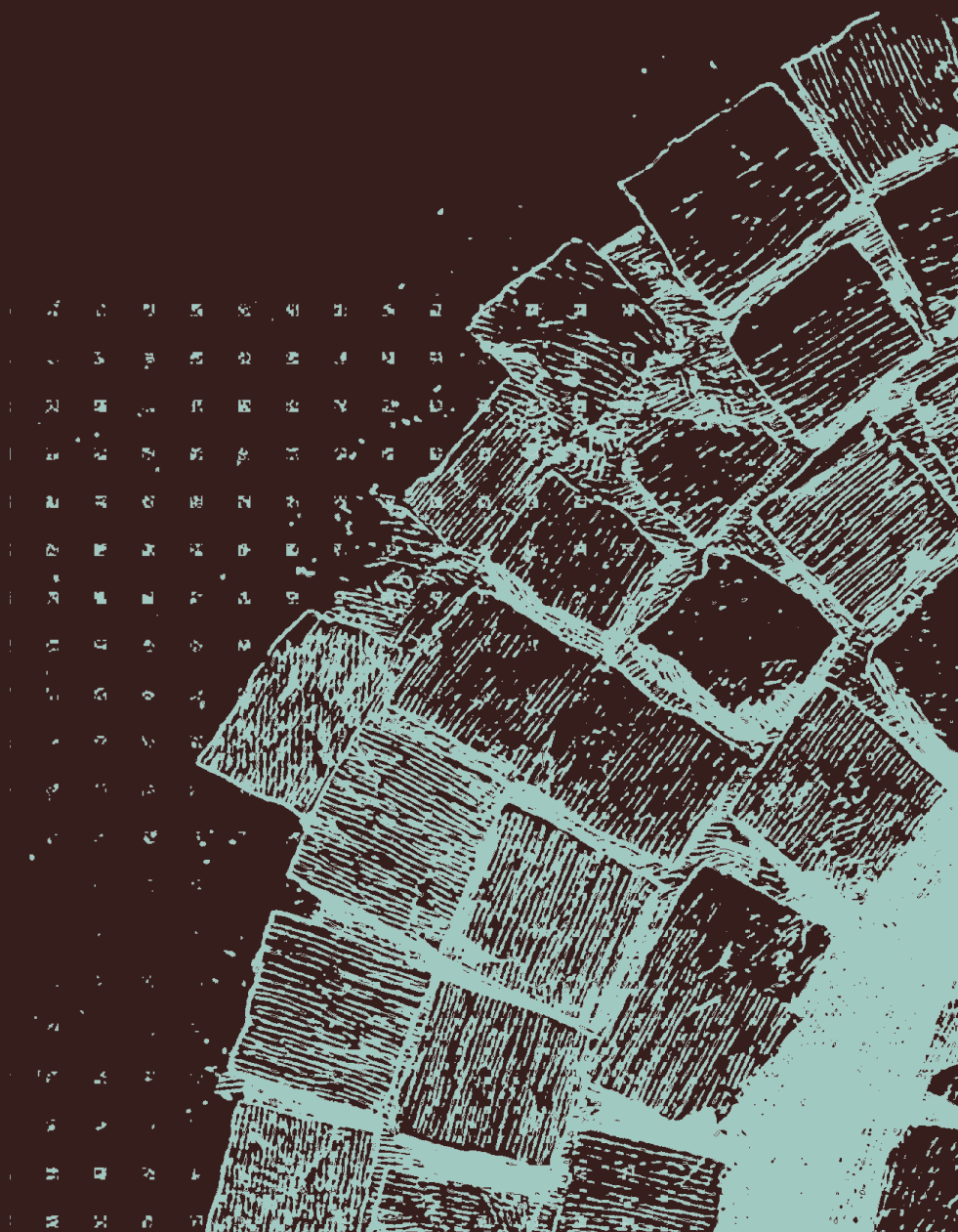
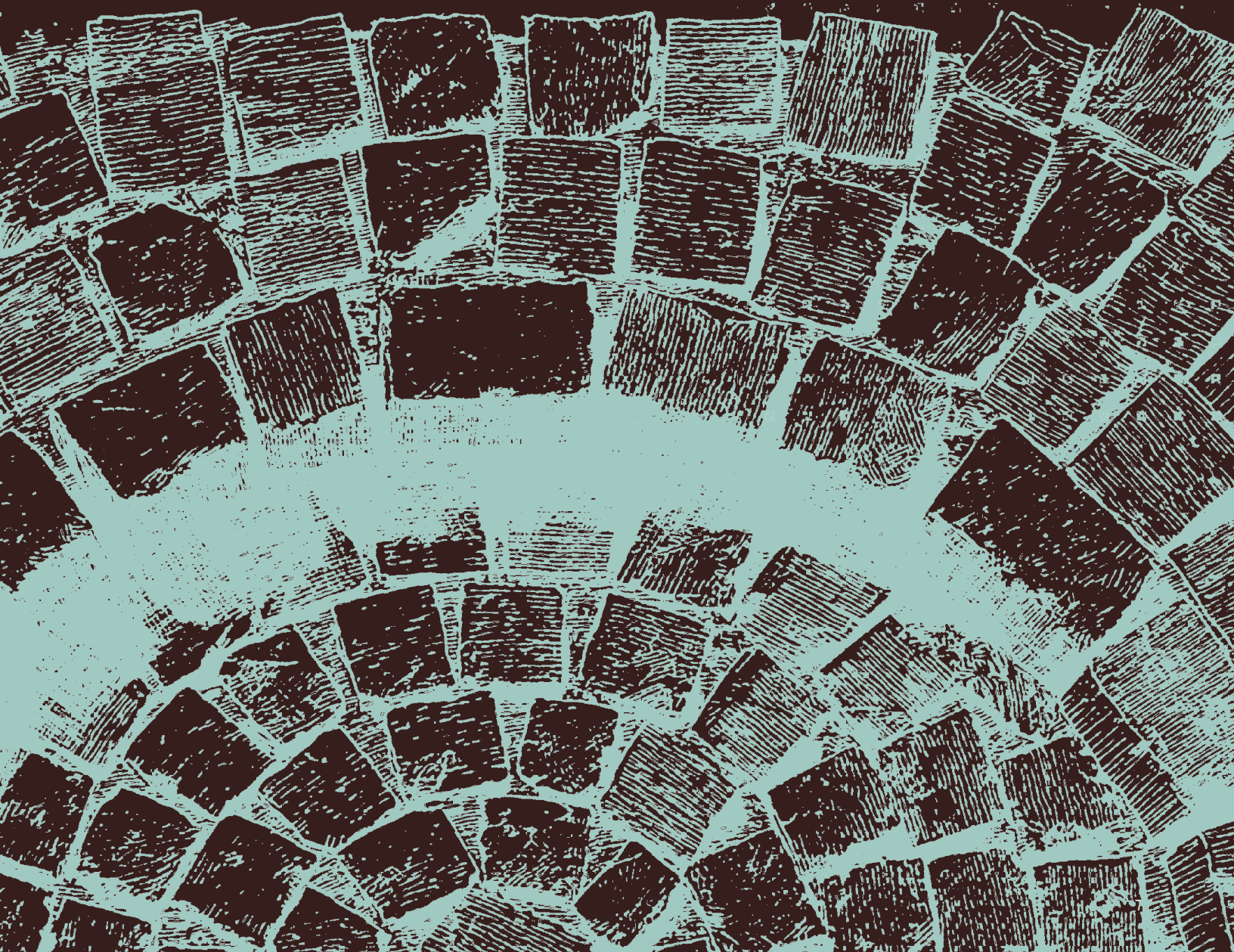


IMAGE SOURCE: MIDJOURNEY

SEPTEMBER 2026



"In many ways, the entire culture of health revolves around the idea that one number can stand in for how far along you are."

IMAGE SOURCE: COOPER HOFMANN VIA UNSPLASH

IMAGE SOURCE: INFINITEFLOW VIA ADOBE STOCK, AI-GENERATED

We usually talk about age as a single number. You blow out one more candle each year and you select a single age bracket on surveys and medical forms. Pediatric growth charts, vaccine schedules, cancer-screening guidelines, and risk scores for heart disease all start by asking the same thing: "How old are you?" In many ways, the entire culture of health revolves around the idea that one number can stand in for how far along you are.

Chronological age is largely interpreted as a kind of master setting for a single process unfolding across the body. At the same time, anyone who has watched a parent's memory stay sharp while their joints disintegrate or seen a friend's heart fail in an otherwise strong body, knows that aging is rarely that symmetrical. Our bodies are made up of dozens of organs, and as we get older some parts clearly give out early while others continue with business as usual.

The new twist is that we are now able to measure that asymmetry. Over the last few years, a wave of research has started to estimate separate biological ages for different organs, effectively resulting in a heart age, a brain age, a lung age, even an immune-system age.[1,2]

What has emerged from those analyses is that your heart, brain, liver, kidneys, and fat are not all the same age. In fact, each seems to be following its own aging trajectory. Put those trajectories side by side and the body starts to look less like a single surface weathering time and more like a mosaic: a series of tiles wearing down at different rates. Once you see the body this way, it becomes hard to look at chronic diseases, risk factors, or even longevity in quite the same terms.

One age on paper, many ages in blood

How can we even estimate how old our organs are? They're tucked away inside the body, and most of the time we only learn they're in trouble when symptoms make it obvious. With recent developments, a 52-year-old person can actually be broken down into organs of different ages: a heart that looks 60, a brain that looks 47, lungs that look 55. Those details come from an accessible source: the blood, and the proteins circulating within it. This information hints at a future where risk is defined not just by "how old you are," but by which parts of you are aging fastest.

Every organ leaves a biochemical trace in the bloodstream. Neurons release synaptic proteins, the heart sheds structural and signaling molecules, the liver and gut secrete enzymes and hormones, immune cells release cytokines. Your blood serves as the interface for depositing resources and receiving both signals and waste from every organ in the body. With modern proteomics, researchers can measure thousands of proteins in the blood at once and, using tissue atlases, link many of them back to the organs that mostly produce them. From there, the logic is fairly straightforward. First, identify proteins that are strongly associated with a given organ (your "organ-identifying" proteins). Second, across thousands of people of different ages, learn how the pattern of those proteins changes with age. And finally, use that pattern to estimate how old each organ appears in a new person, based on the mix of organ-enriched proteins in their blood. The result is not one whole-body biological age but a panel of ages. Subtracting your actual age from each organ's estimate gives an "age gap" for every system, a number that says how much older or younger that organ appears than would be expected for someone like you.

When organ ages are plotted across large cohorts, a broad picture emerges. Many people have organs that roughly match their chronological age. A smaller group has one or more organs that look years older than the rest, and an even smaller group has several organs aging ahead of schedule together. Those differences are not just cosmetic. Individuals with at least one markedly older-than-expected organ have higher risks of death and age-related disease over follow-up than peers whose organ ages line up more closely with the calendar.[1]

For a field that has spent the last decade arguing over single epigenetic clock estimates, this multi-organ view represents an interesting shift in perspective. It doesn't make chronological age or epigenetic clocks obsolete; those remain powerful summaries of how a life has unfolded. But it does suggest that, under the surface of those single numbers, different organs can drift out of sync. And once you start to see those drifts – one organ racing ahead of the others – it becomes natural to ask whether what we call "chronic disease" is, in many cases, where that local aging has gone the furthest.

How proteomic organ clocks differ from traditional epigenetic clocks

At first glance, proteomic organ clocks sound like cousins of traditional epigenetic clocks, but under the hood, though, they are doing something quite different. Epigenetic clocks work by scanning DNA methylation at dozens to hundreds or even thousands of CpG sites scattered across the genome. On a population level, these marks change in fairly stereotyped ways with age in many tissues. Train a model on enough people, and you can predict chronological age, or even future mortality risk, with a fair amount of accuracy. The result is usually a single output: your estimated biological age or how fast you are aging overall.[3,4]

Methylation clocks are powerful precisely because they are broad. They collapse information from many tissues and cell types into one summary statistic. That makes them good at capturing a person's global exposure history (for example, their developmental environment, lifetime stress, smoking history, and metabolic health) but it also means they tell you little about where in the body that signal is coming from.

> **"Traditional methylation clocks are good at telling you whether your aging has been sped up; proteomic organ clocks start to tell you where."**

Proteomic organ clocks ask a more specific question. Instead of "how old is the body as a whole?", they ask "given the mix of proteins in the blood, how old does this particular organ appear?" By focusing on proteins that are strongly enriched in certain tissues, researchers can build separate age models for heart, brain, lung, liver, and so on. Because these models are based on circulating proteins, they tend to be more sensitive to your current physiology – inflammation, injury, subclinical organ damage, medications, changes in metabolism – than to your lifelong exposure history. Traditional methylation clocks are good at telling you whether your aging has been sped up; proteomic organ clocks start to tell you where.

For someone thinking about their own risk, that "where" matters. A single biological age can tell you that you are aging a bit faster or slower than average, but it cannot currently show you which parts of you are outpacing the rest (though eXplainable AI [XAI] clocks show potential to address this). Organ clocks, at least in research settings, begin to point to the specific systems that are out in front. They are not yet ready for routine clinical use, but they represent a shift from treating aging as a single dial to treating it as a set of gauges, one for each organ, that may eventually guide which risks we watch most closely and which interventions are worth the trouble.

Disease as extreme organ aging

Once you start looking at organ ages side by side, a very practical question follows: when your doctor tells you that you are "at risk" for heart failure, cancer, or dementia, is that just another way of saying that a particular organ is aging much faster than the rest of you?

Consider the heart. In the 2023 *Nature* study which introduced this family of proteomic organ clocks, people whose heart age was substantially older than their chronological age (e.g., an "old" heart in an otherwise middle-aged body) had about a 2.4-fold higher risk of developing heart failure over the next 10-15 years than peers whose hearts matched their years, even after adjusting for standard cardiovascular risk factors.[1] In statistical terms, the heart that looked old in the blood was the one more likely to fail later.

For the brain, the story is similar but more sobering. Alzheimer's disease has well-known genetic risk variants. Carrying one copy of *APOE-ε4*, for example, roughly doubles or triples risk, while two copies of the rare *APOE-ε2* variant are unusually protective.5 In large proteomic studies, a very "old" brain score carried about the same increase in Alzheimer's risk as one ε4 allele, and a very "young" brain score was as protective as having two ε2 alleles.[6] In another large cohort, each step toward an older-than-expected brain was linked to a clear uptick in dementia risk, independent of age and the usual vascular culprits.[7] In other words, how old your brain looks in the blood can matter as much as some of the strongest common risk factors we know of.

Lungs show the same pattern. In UK Biobank data that combine breathing tests and imaging with organ-age models, people whose lungs looked older than expected for their age were more likely to have chronic lung diseases like COPD – and also more likely to die over the next decade – than people whose lungs looked on-schedule, even when obvious lung disease was not yet present.[2]

Why should any of this matter to someone who is not designing risk models for a living? Because it reframes what "being at risk" means. Instead of thinking of heart failure, dementia, or lung cancer as separate lightning strikes, you can think of them as what happens when aging in one organ runs far ahead of the rest of the body. If future clinics can see, from a blood test, that your heart or brain is aging out of line years before symptoms start, prevention suddenly has a much more concrete target.

There are important caveats. These studies are observational. Having a predicted "old" brain does not prove that making the brain "younger" would prevent dementia, any more than lowering cholesterol guarantees you will never have a heart attack. Some of what the clocks see is almost certainly very early, pre-symptomatic disease that has already begun to change the blood. But taken together, the pattern is hard to ignore: look for the organs that appear oldest, and you rediscover the organs where disease is most likely to show up later. It is no longer only "which organ is aging fastest?", but also "what happens to the rest of the body when one organ pulls

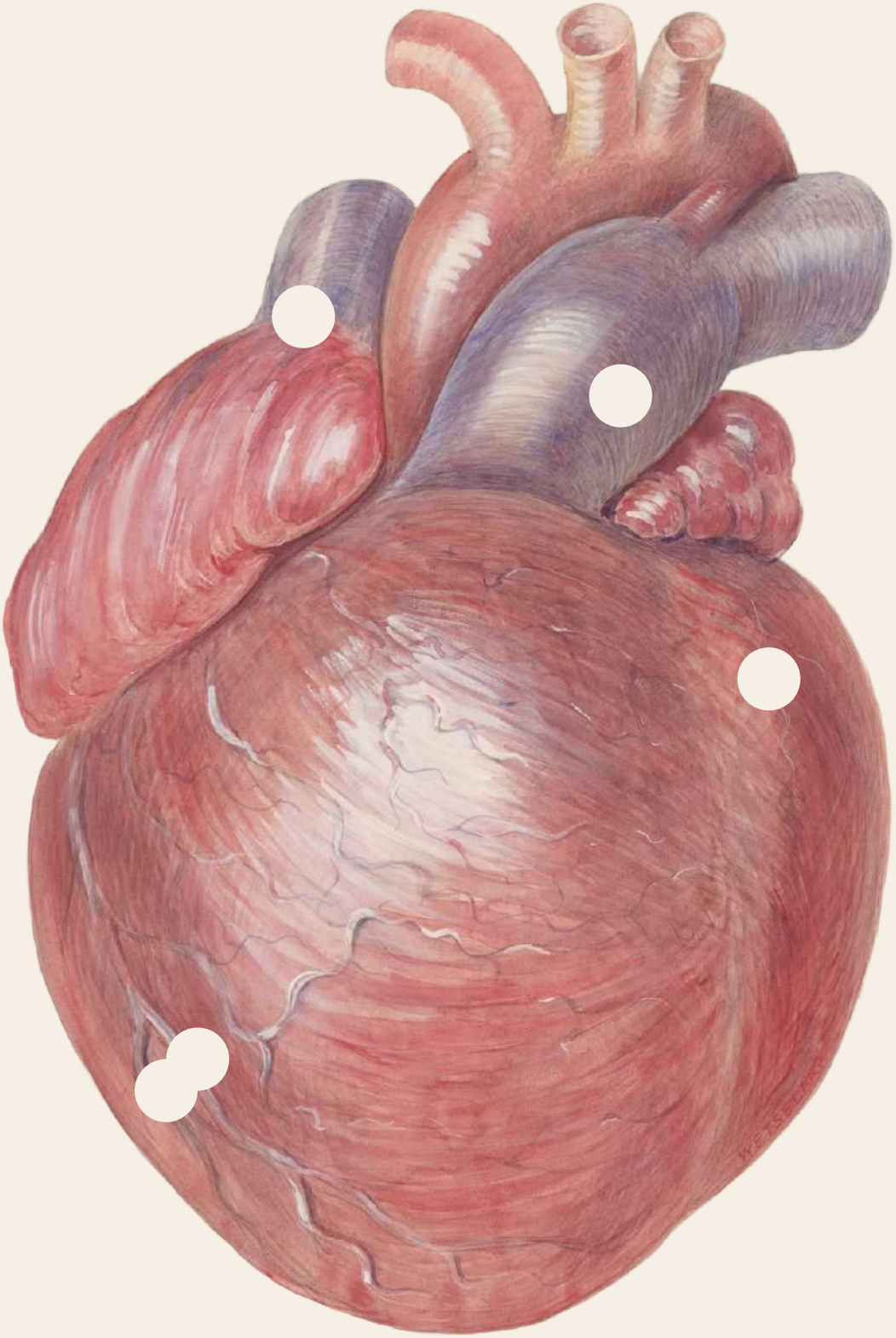


IMAGE SOURCE: EUROPEANA VIA UNSPLASH

"Instead of thinking of heart failure, dementia, or lung cancer as separate lightning strikes, you can think of them as what happens when aging in one organ runs far ahead of the rest of the body"

ahead?" In other words: if one part of the mosaic is aging out of line, does that aging start to spread?

Is aging contagious between organs?

If you zoom out from one organ at a time and instead ask how organ ages relate to each other, the picture becomes more like a network. In large imaging- and proteomics-based studies with thousands of participants, a few high-level patterns pop out.

The first is that no organ is an island. People whose hearts look older than expected often have slightly older-looking kidneys, lungs, or brains. Accelerated aging in one organ tends to co-travel with acceleration in others, forming what some call a "hidden aging network." Certain organs (especially the heart and lungs) appear as hubs, meaning that when they are old for age, the rest of the network is more likely to look older too.[2]

The second is that how many organs are old matters as much as how old any single organ is. People with one fast-aging organ had somewhat higher risks of death and major disease. People with several fast-aging organs had much steeper risks; the danger climbed roughly in step with the number of organs that were ahead of schedule.[2] These patterns are still correlational, but they point to something intuitive: organs talk to each other. They share blood, hormones, nerves, and immune cells. When one ages rapidly or fails, the fallout is system-wide.

How your organs talk to each other

Aging organs release different mixes of inflammatory and metabolic byproducts into the circulation. Chronic heart failure, for example, floods the body with signals of stress and congestion. Adipose tissue secretes pro-inflammatory cytokines and fatty acids. These circulating factors can stress distant tissues, disrupting their function and repair.[8] The immune system itself ages, a process called "inflammaging". Old or dysregulated immune cells respond less efficiently to pathogens and vaccines, but remain chronically activated, producing cytokines that damage blood vessels, joint cartilage, and brain tissue. Immune aging shows up in both proteomic clocks and disease statistics as a powerful common driver across many organs.[9,10]

In this sense, the question "is aging contagious?" within the body is not as strange as it first sounds. An aging heart changes the biochemical weather for the kidneys and brain, an aging immune system changes the quality of inflammation everywhere, an aging brain changes how every organ is controlled.[11] These kinds of interlocking feedback loops are the connection points where aging in one system starts to shape the fate of others.

So far, all this evidence comes from watching people over time with blood tests and scans. We see patterns that suggest organs are influencing one another, but we are still observing from the outside rather than directly testing the signals themselves. To get closer to that, scientists have turned to some of the strangest experiments in modern biology.

IMAGE SOURCE: RADOSNASOSNA VIA ADOBE STOCK

Shared blood, shared age?

If you have been following aging science for a while, you may have seen an unnerving picture: two mice, one young and one old, stitched together along their flanks so that they share a blood system. This procedure, called "heterochronic parabiosis", has been used off and on for more than a century to study hormones and immune responses. Over the past two decades, it has re-emerged as a test of what a younger or older systemic environment can do to aging tissues.[12,13]

Across many of these experiments, old mice partnered with young ones show a consistent pattern of benefits. Their stem and progenitor cells behave more youthfully: muscle satellite cells regain the ability to proliferate and repair injured muscle, and liver progenitors divide more readily.[12] In the brain and vasculature, young blood improves production of new neurons, learning and memory, and even restores aspects of blood-brain-barrier integrity in aged animals.[14–16] At the molecular level, old mice attached to young mice show reduced burdens of zombie-like senescent cells, lower inflammatory signaling, and molecular patterns that shift back toward youth across multiple tissues.[17–19] In some protocols, long-term pairing followed by separation even modestly extends the median lifespan and healthspan of the old mice.[19]

Those findings were intoxicating enough to fuel a mini-mythos around "young blood," and a flurry of stories about start-ups and early adopters acquiring plasma from younger donors.

Other lines of evidence have cooled some of that excitement. When researchers extended heterochronic parabiosis for three months and then detached the animals, the old parabionts did not gain dramatic extra years of life, and the young parabionts actually lost lifespan compared with young mice joined to other young mice.[20] Simpler "blood-exchange" experiments, which swap blood between animals without sewing them together, show that a single exposure of young mice to old blood is enough to increase markers of cellular aging and functional decline in multiple tissues.[21] The overall picture is that old blood is very good at pushing young tissues toward an older state, and while young blood can rejuvenate many aspects of old tissues it is certainly not a life-extension strategy in itself.

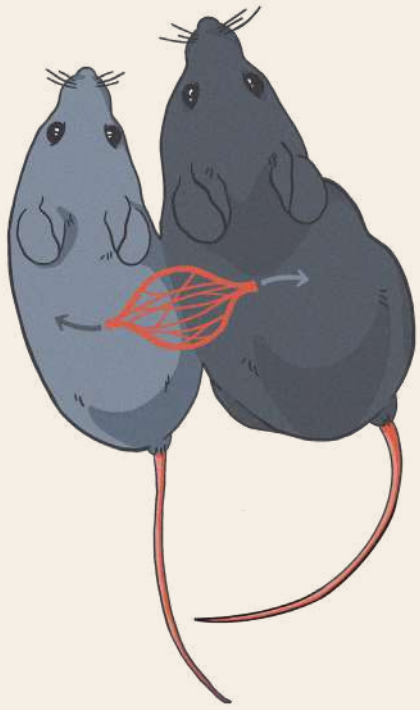


IMAGE SOURCE: JACQUELYN LICHTER

Borrowed age: What transplants reveal

Heterochronic parabiosis is such an extreme intervention that it is hard to map directly onto the human experience. No one is going to stitch pairs of 30- and 70-year-olds together for the sake of science. But the underlying question of how much tissue age is determined from within, and how much is imposed by the body it lives in, can be asked in gentler ways. One of the clearest comes from a recent experiment in transplanted fat.

In that study, researchers took white adipose tissue from young mice and grafted it into old mice, and vice versa, then tracked how "old" the grafts looked over time.[22] If tissue age were entirely intrinsic, young fat should stay young in an old host and old fat should stay old in a young host. Instead, the grafts largely adopted the age of their new home. Young fat implanted into old animals rapidly acquired an older molecular profile: its clocks ticked upward until it closely resembled the host's native old fat. Old fat placed into young animals moved in the opposite direction, shifting toward more youthful gene-expression programs.[22]

In this model, old bodies drag young grafts up toward their age, while young bodies pull old grafts partway back down. This result aligns with what the organ-clock studies are telling us: organ aging is both local and shared. Each tile in the mosaic has its own age, history and vulnerabilities, yet all of them live in the same systemic environment, which can nudge their biology toward older or younger states.

This raises a more philosophical question: if evolution could, in principle, make tissues more or less sensitive to systemic aging cues, why are we built as such uneven mosaics in the first place?

Why is aging mosaic at all?

To see why organ-by-organ aging makes sense to biologists, it helps to zoom out to evolution for a moment. Evolution by natural selection is, at its core, a filter: traits that help organisms survive and have children tend to become more common in the population, and traits that get in the way tend to disappear.

The key point is when this filter is strongest. Natural selection mainly cares about what happens from birth through the years when you can have and raise children. Once that stage of life is over, selection gets much weaker. A genetic change that slightly increases your chance of having children at 25 but also increases your chance of a stroke at 75, can still spread through the population because the benefit shows up early and the cost shows up late.

This basic rule applies differently to different organs. Some systems are essential for surviving to and through the reproductive years: the brain, the heart, the immune system, the reproductive organs. Evolution has been under strong pressure to keep those working reasonably well through youth and midlife, so they are built with more robust maintenance and repair. [23] Other parts of the body are less critical from this narrow, early-life perspective. The cartilage in your knees, for example, mostly needs to function while you are growing, working, and raising kids. Ovaries, as I've written previously, are tuned for a reproductive lifespan that does not extend into modern expectations of eight or nine decades of life.

On top of this, maintenance has a cost: repairing DNA damage, replacing worn-out cells, and running a careful immune system all burn energy. In the environments in which humans evolved, the body could not afford to give every organ top-tier

upkeep indefinitely, so some systems were simply "budgeted" more heavily than others.

Put these ideas together and the mosaic starts to make sense. Some organs get relatively generous maintenance budgets through midlife, while others get just enough to get the job done in youth. There was never much evolutionary pressure to keep all organs in lockstep into our 70s and 80s. What mattered was that the overall package worked well enough during the years when genes are passed on, not whether your brain, joints, and kidneys would all be the same biological age decades later.

Seeing our bodies as products of evolutionary trade-offs rather than machines designed for lifelong uniformity can help set expectations. We are not dealing with a single aging program that can be slowed evenly everywhere. We are dealing with many systems, each with its own history and level of maintenance, now asked to function far longer than the conditions they were shaped for.

The mosaic body in medicine

Most of us are not going to walk into a clinic next year and be handed a tidy printout labeled "brain 61, heart 55, kidneys 49." Proteomic organ clocks are still largely research tools. Imaging-based organ ages require scanners and software that are not part of standard care. Parabiosis will (thankfully) remain confined to mice.

Even so, this way of looking at the body is already shaping how scientists think about aging. Organ-specific ages give researchers a way to target risk and test interventions more precisely. Instead of enrolling a broad swath of "people over 65" into a clinical trial, future studies could focus on those whose vascular or brain ages are especially advanced, or track whether a candidate therapy slows aging of the organ it is meant to protect. Similarly, organ aging burden (the number of fast-aging organs) could be used to identify people who might benefit most from more monitoring or prevention.

For clinicians, these tools raise a different kind of challenge. What does it mean to tell a 55-year-old person with no symptoms that her brain looks 70 by a proteomic clock, or that his lungs are biologically older than his heart? How do you talk about that information without tipping people into anxiety or fatalism? How do you protect patients from commercial overreach, where organ-age readouts might be packaged into glossy but unvalidated "longevity" offerings?

There are also, unsurprisingly, concerns about equity and generalizability, as much of the data underpinning these clocks comes from cohorts which are not fully representative of global diversity. If organ age scores become part of risk prediction or eligibility for expensive drugs, they could entrench existing inequities into yet another layer of algorithm. Making these tools fair and reliable across different groups of people will require doing the important work of building clocks in more diverse populations and testing how well they perform across settings.

The mosaic framing offers a kind of grounding. It reminds us there is no single age to outrun, no one clock to hack. You carry a constellation of ages inside you, some already old for your years, others still young. And if you've read any of my previous articles, you can probably guess the punch line. The most reliable levers we have for shifting the distribution of organ ages are familiar: controlling blood pressure, not smoking, building and keeping muscle, getting your heart rate up with physical activity, managing blood sugar, sleeping well, getting vaccinated. Good daily habits do not care how old your organs are.

Organ age work slots into a larger landscape of ideas about why we age. Some theories emphasize damage accumulation (DNA breaks, misfolded pro-

teins, mitochondrial wear), others frame aging as a gradual loss of the information that keeps cells behaving like themselves. A fundamental hypothesis in the longevity field ties these threads together: whatever mix of damage and information loss is at play, the same underlying processes drive both the everyday changes we call "normal aging" and the major diseases of later life, and slowing those processes should, in principle, lower the risk of many conditions at once. The mosaic view localizes these ideas, showing that damage and information loss do not strike the body evenly, and disease is where a local breakdown crosses a threshold.

Thinking this way suggests a more targeted version of "slowing aging." Instead of asking whether we can rewind the whole organism, we can ask which organs are losing function and information fastest, whether we can stabilize those systems, and how that, in turn, reshapes the network of organs attached to them. Perhaps a narrower ambition than global rejuvenation, but certainly a more realistic one.

This work is still in its early stages. Most current organ clocks were designed to predict chronological age, not to tell us which interventions are safe in humans. Mouse-sewing and fat-graft experiments show that changing the systemic environment can pull tissues toward older or younger molecular states, but they do not yet offer roadmaps for doing so safely at scale. What these tools do give us, for now, is a clearer map of the problem.

A generation ago, aging in medicine was mostly treated as background noise to be controlled for so we could focus on "real" diseases. Today, organ-specific clocks and related tools are pushing aging itself into the center of the story. They may not tell us how to rebuild the mosaic from scratch, but they can help us see which tiles are wearing fastest and give us a better shot at keeping the whole pattern intact for longer.

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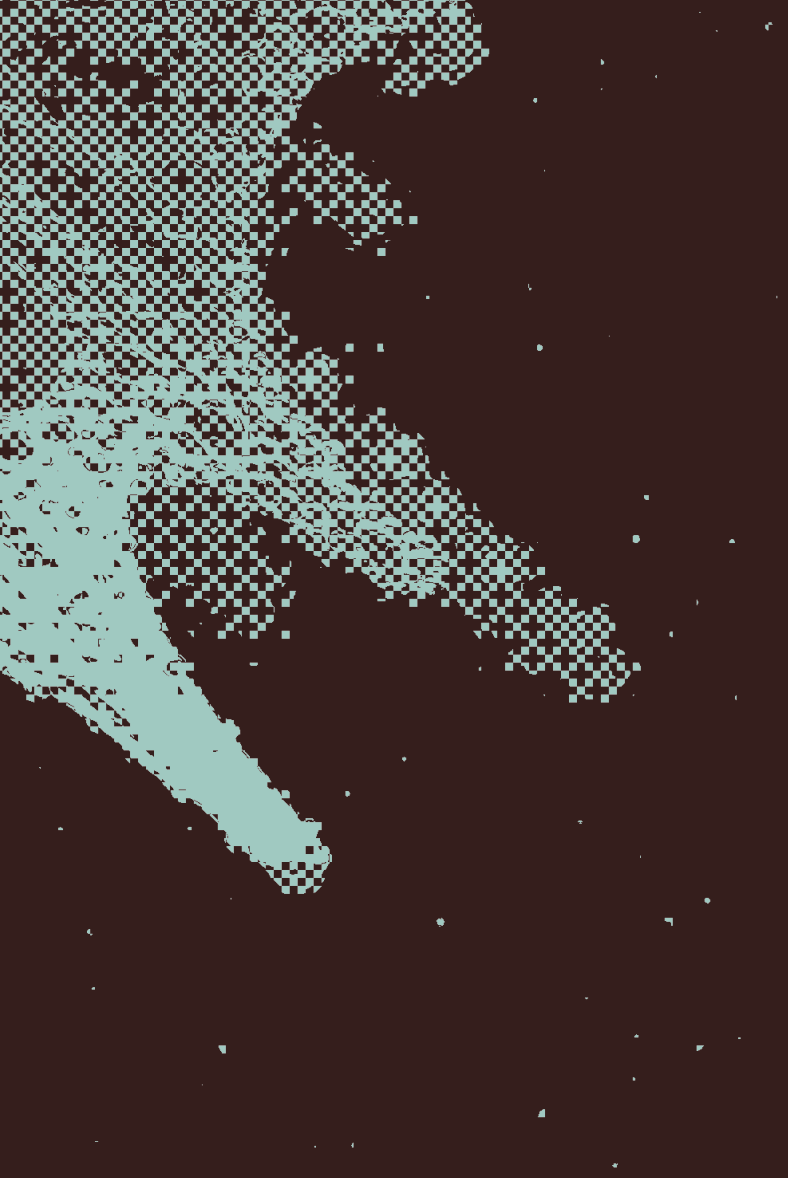
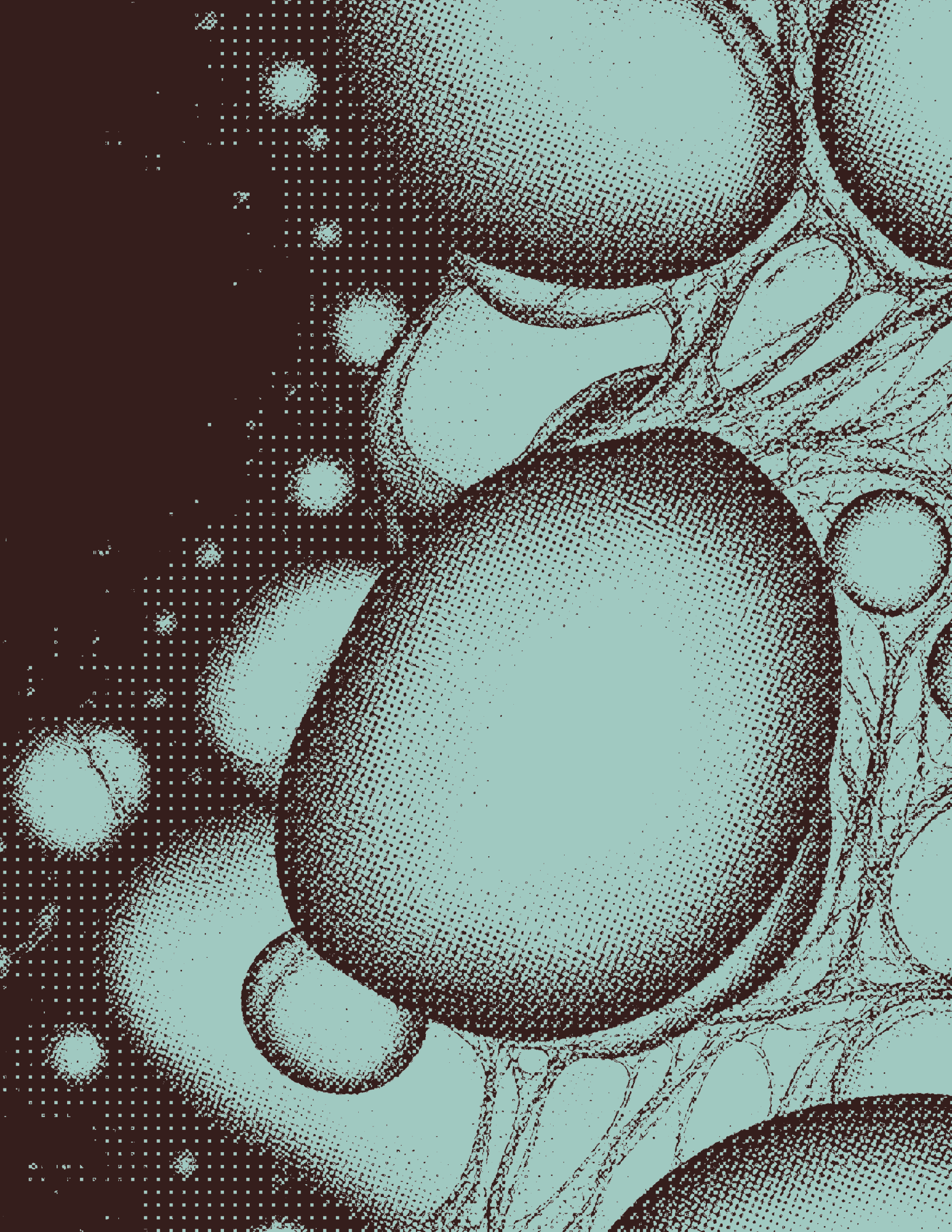


DEATH BY FAT: HOW TO KILL A ZOMBIE CELL

IMAGE SOURCE: MIDJOURNEY

BY DAVID A. SINCLAIR, AO, PHD



In the early 20th century, science and medicine largely viewed fats as a dense source of calories and nothing more. In 1929 and 1930, two papers published by a married pair of researchers turned this worldview on its head. The authors, Dr. George and Mildred Burr, showed that rats given a fat-restricted diet developed a slew of ghastly health problems and succumbed to early deaths. The Burrs introduced the phrase "essential fatty acids" and demonstrated, unequivocally, that fats represent a critical source of nutrients.[1]

Despite their findings, the bad reputation for fats began to grow throughout the 20th century as research linked diets high in saturated fat with heart disease. The Seven Countries Study by Dr. Ancel Keys and his collaborators was particularly influential, revealing a strong relationship between saturated fat intake and the risk of cardiovascular disease.[2] While saturated fat is indeed a known causal risk factor for atherosclerosis, these findings were not universally met with nuance. In 1977, for example, the United States Senate Select Committee on Nutrition released national guidelines that broadly recommended cutting down fat intake. The guidelines specifically encouraged Americans to "reduce fat consumption from over 40% down to 30% of energy intake".[3]

This lack of nuance led to a broad vilification of fats and a marketing frenzy. The low-fat food industry flourished, with companies turning to sugar and other carbohydrates to replace fat content. Claims like "fat-free" and "half the fat" became a central marketing strategy. They told consumers fat was something to avoid, even when the overall nutrition of the product wasn't necessarily healthier. The irony was that, in their attempt to avoid fats, many people were consuming more unhealthy, processed carbohydrates, which research later linked to increased rates of obesity, diabetes, metabolic syndrome, and other chronic diseases.

Fast-forward to today and healthy fats are now all the rage. There's the SMASH (salmon, mackerel, anchovies, sardines, and herring) acronym for fatty fish rich in the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Walnuts, chia seeds, and ground flax seed represent robust sources of the omega-3 fatty acid alpha-linolenic acid (ALA) and are frequently added to smoothies, yogurts, or other dishes to boost nutritional value. It is also now well-known that certain fats, like omega-3s, cannot be made by the human body and must come from the diet.

There has been a growing awareness that certain fats likely play a vital role in health and aging, with many different fats extending lifespan and impacting age-related health in laboratory animal models.[4] Thanks to a new paper spearheaded by the University of Minnesota professors Dr. Paul Robbins and Dr. Laura Niedernhofer, that awareness has become even stronger.[5]

In this study published on April 20th, 2026 in a new Cell Press journal, *Cell Press Blue*, the authors screened the ability of different fats to kill senescent cells, sometimes colloquially referred to as "zombie cells." These are cells that, in response to certain kinds of damage or their telomeres (protective caps on the ends of chromosomes) becoming too short, stop dividing but continue to hang around. While senescent cells can play critical roles in wound healing and cancer resistance,[6] they tend to accumulate with age are a well-established hallmark of aging.[7] Like an unruly guest who refuses to leave well after the dinner party has ended, they can cause substantial harm by spewing out inflammatory chemicals into their environment.

The authors of this new paper identified a lesser-known fat that was surprisingly effective at taking out senescent cells. The fat, called α-eleostearic

acid (α-ESA), is found in seeds from various plants. Seeds from *Momordica charantia*, commonly known as bitter melon, are especially rich in α-ESA.

When α-ESA or a chemical derivative called α-ESA-me were given to older mice, the burden of senescent cells within the brain and other tissues was significantly decreased. The effects of α-ESA-me were also tested using a specialized mouse model of accelerated genomic and epigenomic instability that Dr. Niedernhofer has studied for two decades.

Administered orally three times a week, α-ESA-me reduced the number of DNA-damaged cells and enhanced healthspan. Notably, a composite score that measures the severity of aging symptoms through traits like grip strength, gait abnormalities, spinal curvature, and other common aging indicators, showed significant improvement.

How exactly did α-ESA kill zombie cells? The authors discovered that α-ESA caused senescent cells to die through a process called "ferroptosis," a term derived from the Latin word *ferrum* (iron) and the Greek word *ptosis* (falling). This form of cell death is triggered by iron and an excess of cell-damaging free radicals.

Although the study was conducted in an animal model, it is still an impressive and surprising discovery: A natural, plant-derived fat that eliminates senescent cells and alleviates aspects of aging in mice. Beyond giving health enthusiasts another reason to embrace the potential of healthy fats, this paper lays the foundation for further research aimed at translating natural molecules into effective medicines that target aging biology.

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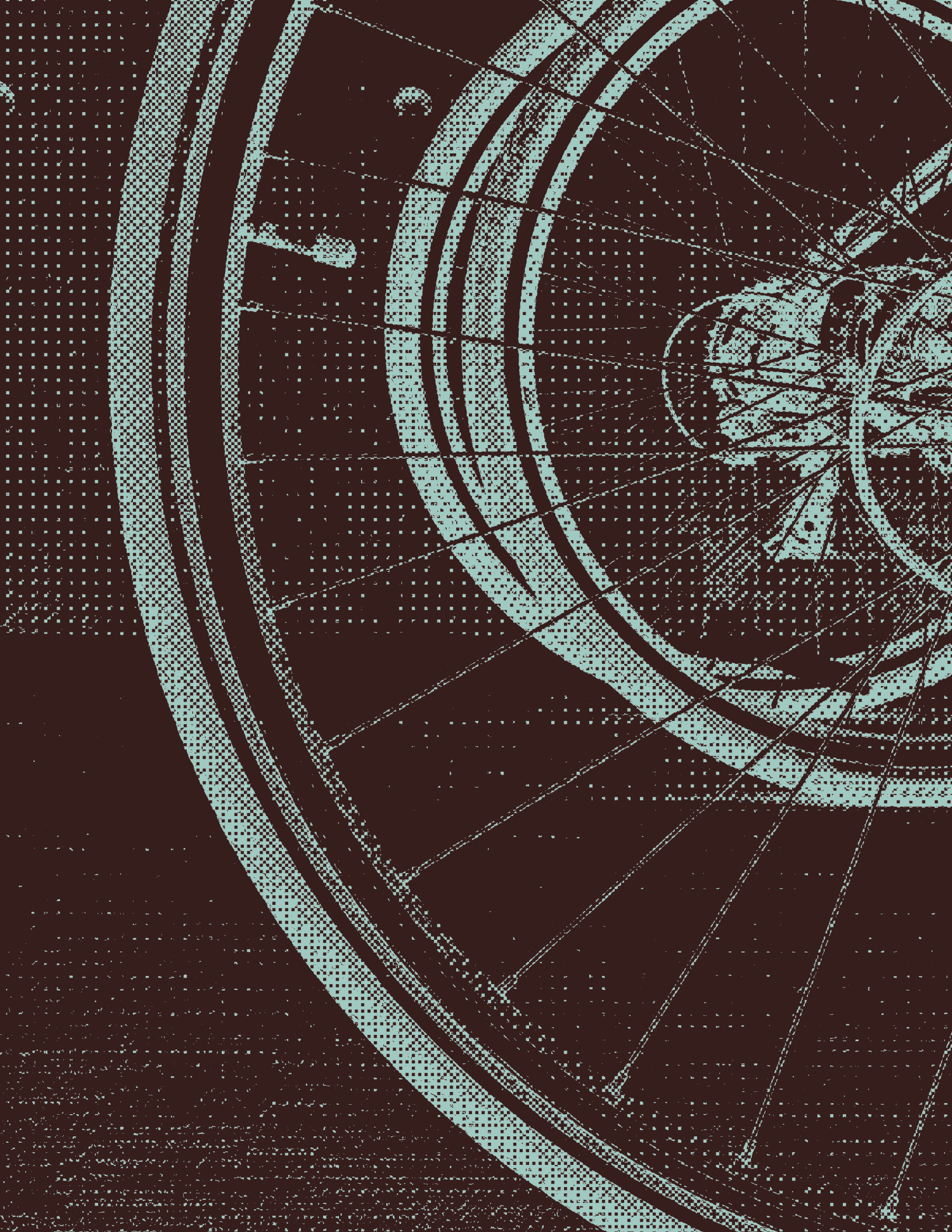
A BIKE RIDE A DAY KEEPS THE GRIM REAPER AWAY

IMAGE SOURCE: MELISSA THIGPEN VIA UNSPLASH

BY ADIV JOHNSON, PHD



In 44 BC, the Roman scholar and great orator Marcus Tullius Cicero wrote a philosophical essay called *Cato Maior de Senectute* ("Cato the Elder On Old Age") at the age of 62. The piece itself centers around a statesman named Cato, who argues that it's entirely possible to remain dignified and productive in old age. Through Cato, Cicero insists that we have a duty to maintain ourselves as we experience the passage of time. He prescribed eating in moderation, taking care of the mind, and staying physically active.

More than 2,000 years later, the recommendation for physical activity is one that longevity scientists fervently agree with. Exercise, possibly more so than diet or sleep, is one of the most powerful tools we have at our disposal to promote healthy aging. Resistance training and cardiovascular exercise can do wonders for optimizing how long we live and, more importantly, how much of that life is spent in good health.

There's a very large body of scientific evidence showing that exercise can promote longevity and combat the hallmarks of aging.[1] People with a higher aerobic capacity are also much more likely to live longer than people with a low aerobic capacity. In one study, people with low cardiorespiratory fitness were 404% more likely to die in the follow-up tracking period than those in the elite fitness category.[2]

In research published earlier this year in the journal *GeroScience*, the evidence that we should all be moving our bodies became even more compelling with a new paper from Dr. Tim De Meyer and team at Ghent University in Belgium.[3]

The authors enrolled 42 adults aged 35-65 years for a six-month endurance exercise intervention centered on cycling. The primary outcomes were improvements in body composition and VO2 max, the latter of which is an aging biomarker that reflects aerobic capacity.

At baseline, the average adhering participant had a BMI of 26.7 kg/m2 (which is in the overweight range) and a body fat percentage of 33.8%. After six months of endurance cycling exercise, the participants significantly improved their VO2 max (+19.8%), peak power output (+23.3%), and pulse wave velocity (-5.4%). Both BMI and body fat percentage also significantly declined.

While this is all interesting, it's not unexpected given what we know about exercise and its many benefits. What makes this recent paper more notable is that they also looked at a unique biomarker with the fairly foreboding name GrimAge, a machine learning model that strongly correlates with age.[4] GrimAge is based on DNA methylation, a process our cells use to help control gene expression. By adding and removing chemical methyl groups to specific regions of DNA, regions of DNA can be effectively opened up or closed off. GrimAge and models like it are known as epigenetic aging clocks.

IMAGE SOURCE: MIDJOURNEY

The name GrimAge is based on the fact that the model was trained so that its output is strongly associated with the future risk of death in adults tracked over time. In the original study introducing GrimAge, every one-year shift in predicted age corresponded to a 10% change in the likelihood of dying from any cause in the future.[4]

After six months of cycling, average GrimAge dropped from +0.33 years to -0.29 years. This reduction of 0.62 years is not trivial, especially given that six months of chronological aging had gone by. In addition to improving mood, boosting cardiovascular health, and offering many other benefits, we can now add setting back GrimAge to the large list of perks offered by aerobic exercise.

So, if you haven't already and can squeeze it in today, try to make time for a bike ride, walk, run, or any other kind of physical activity.

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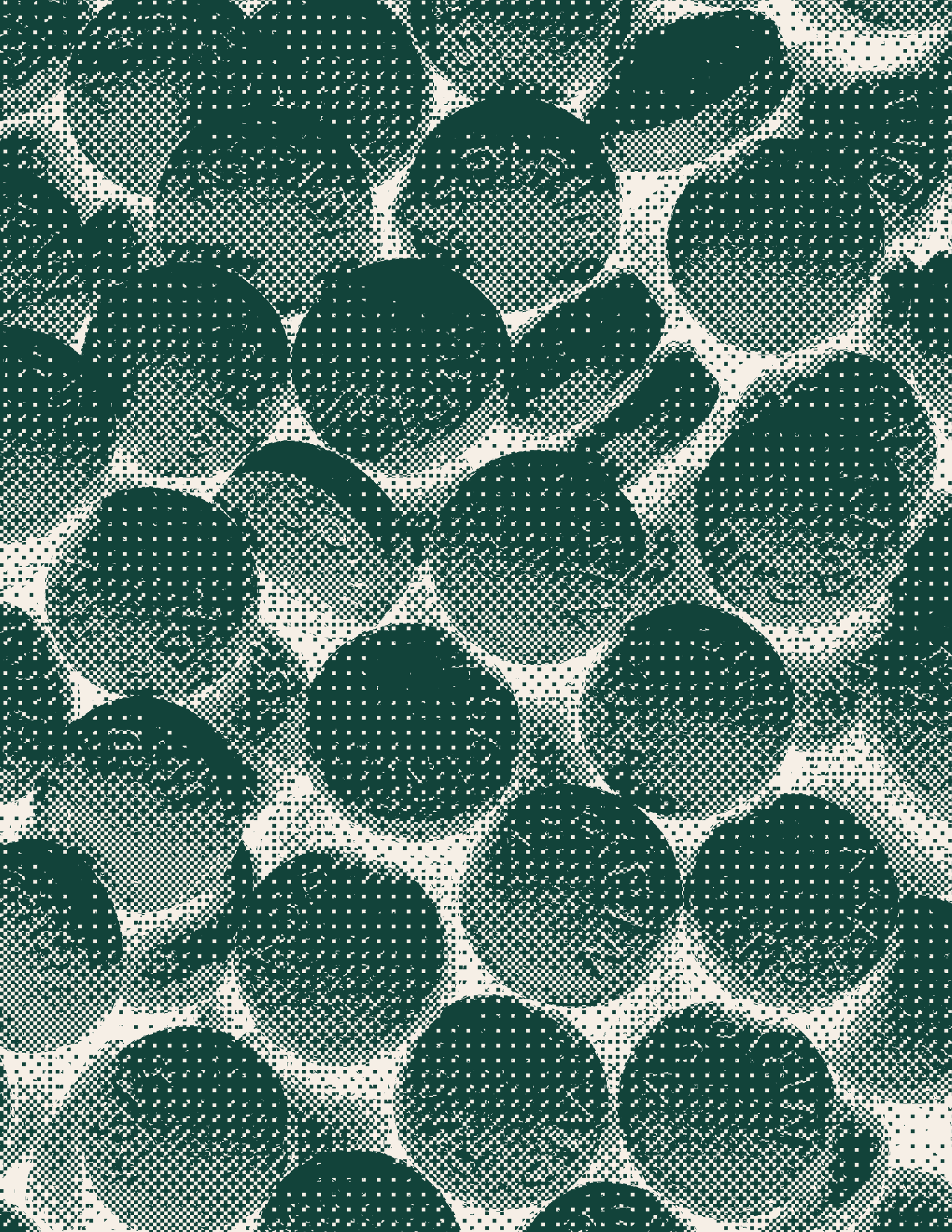
OPINION

DAILY ASPIRIN: THE STORY ISN'T OVER

BY DAVID A. SINCLAIR, AO, PHD

IMAGE SOURCE: AI-GENERATED WITH OPENAI



One of the biggest challenges in medicine is that most people, including many physicians, don't read scientific papers. Instead, they learn about scientific breakthroughs through colleagues, journalists, TV commentators, podcasters, social media influencers, and increasingly through algorithms that reward outrage, certainty, and simplicity.

The problem is that science is rarely simple.

A nuanced study showing that a drug may help some people, harm others, and depend heavily on age, gender, genetics, and lifestyle often emerges from the media machine as a headline declaring that the drug either works or doesn't. The history of medicine is littered with examples. Coffee is good for you, then bad for you, then good again. Eggs are dangerous, then healthy. Fat is the enemy, then sugar is the enemy. Hormone replacement therapy is beneficial, then harmful, then beneficial again. Eat plants. No, eat mostly animals. Aspirin may be one of the most consequential examples.

For much of the late twentieth century, millions of people took a daily aspirin believing it would prevent heart attacks, strokes, and perhaps even help them live longer. Then came a wave of studies, revised guidelines, and a flood of headlines announcing that aspirin no longer worked, was too dangerous, or should be abandoned altogether. The message reached the public with remarkable clarity. Unfortunately, it was also misleading.

What many people heard was that aspirin had gone from a lifesaver to a mistake. What the studies showed was far more nuanced. Aspirin had not stopped preventing heart attacks. It had not suddenly become unsafe. Rather, as cardiovascular medicine improved and heart attacks became less common, the balance between benefit and risk shifted for certain groups of people. The biology had not changed. The context had.

Lost in much of the coverage was evidence that aspirin may reduce the risk of colorectal cancer, lower recurrence rates in some genetically-defined subgroups, and provide disproportionate cardiovascular benefit in people with elevated lipoprotein(a), or Lp(a), one of the strongest inherited risk factors for cardiovascular disease. Lp(a) is a particularly sticky molecule that is prone to getting stuck in arterial walls and forming plaques.

Evidence has continued to accumulate that aspirin may be particularly valuable for genetically-defined groups at elevated cardiovascular risk, especially individuals with high Lp(a) levels.[1,2]

Yet despite these findings, routine aspirin use remains controversial because the bleeding risk is immediate while many of the potential benefits may take years to emerge. The public was told a simple story: aspirin = bad. The science told a far more complicated one. Aspirin may be harmful for some people, beneficial for others, and increasingly useful when guided by genetics and individual risk.

In other words, the story of aspirin is far from over. If anything, it is becoming more interesting.

Long before pharmaceutical companies existed, ancient civilizations were using preparations derived from willow bark to reduce pain and fever. References appear in literary works from Ancient Egypt and Greece, including Hippocrates, who prescribed willow extracts for pain and childbirth discomfort.[3,4]

By the late nineteenth century, the active compound, salicylic acid, had become a widely used treatment for rheumatic diseases and pain, though its gastric side effects often limited its use. Patients frequently developed nausea, gastric inflammation, and bleeding. Chemists searched for

a way to preserve the therapeutic effects while reducing the toxicity.

That breakthrough came in 1897 when Dr. Felix Hoffmann, working at Bayer, synthesized acetylsalicylic acid in a pure and stable form.[3–5] Two years later, Bayer trademarked the name Aspirin. The "a" came from acetyl, while "spir" was derived from *Spiraea ulmaria*, a common European plant used to flavor drinks like mead and a source of salicylates before modern synthesis. Aspirin became so famous that, in many countries, the brand name eventually became the generic name itself.

> **"The 81 mg recommendation may be one of the most influential historical rounding errors in medicine."**

By the early twentieth century aspirin had become a global phenomenon. It was prescribed for headaches, arthritis, fever, and a remarkable range of everyday ailments. Then in the 1950's physicians began noticing something unexpected: patients taking aspirin seemed less likely to suffer heart attacks. At first this observation was difficult to explain. Aspirin was viewed primarily as a painkiller. The idea that it could prevent cardiovascular disease seemed almost accidental. The key turned out to be platelets, which help form clots.

Aspirin irreversibly inhibits the production of a signaling molecule that promotes platelet aggregation.[6] Since many heart attacks occur when an atherosclerotic plaque ruptures and triggers sudden vascular clotting, aspirin's effect on platelets provided a plausible biological explanation for its cardiovascular benefits. The discovery transformed aspirin from a useful medicine into a scientifically understood one and helped earn Dr. John Vane a share of the Nobel Prize in Physiology or Medicine in 1982.[7]

A clinical revolution followed quickly. One of the pivotal figures was Dr. Peter Elwood, whose studies in the 1970s helped demonstrate that aspirin could reduce recurrent heart attacks and cardiovascular deaths[8] and by the 1980s, aspirin had become a cornerstone of cardiovascular prevention. It was inexpensive, widely available, and remarkably effective. For patients who had already suffered a myocardial infarction, the evidence became overwhelming. Aspirin saved lives, and cardiologists embraced it. Physicians recommended it routinely. Millions of people adopted the daily aspirin habit.

One of the stranger stories in medicine is why American doctors settled on 81 mg aspirin rather than 80 mg or 100 mg, even though doses between roughly 75 and 100 mg produce similar antiplatelet effects in most people. The answer has little to do with biology and all to do with history. A standard aspirin tablet was once 5 grains, or about 325 mg. A "grain" is an old-fashioned unit of measurement. When physicians began prescribing lower doses, they often recommended one-quarter of a tablet, 1.25 grains, which converted to roughly 81 mg. The number stuck, showing medical practice is not always an exact science and can be heavily influenced by past behaviors.

The 81 mg recommendation may be one of the most influential historical rounding errors in medicine.

So why did doctors stop recommending this drug? It was not that aspirin didn't work. What happened was that between 2000 and 2020, age-adjusted heart disease mortality in the United States fell by nearly 40%. Statins, ezetimibe (Zetia), and PCSK9 inhibitors reduced low-density lipoprotein (LDL) cholesterol to levels cardiologists once considered almost unattainable. At the same time, smoking rates de-

clined, blood pressure control became routine, and emergency treatment of acute coronary syndromes became far more effective. And this changed the mathematics of prevention.

Studies with names like ARRIVE, ASCEND, and ASPREE all examined aspirin in populations that historically would have been considered candidates for primary prevention.[9-11] For example, the ASCEND trial showed that in people with diabetes, aspirin reduced serious vascular events but also increased major bleeding, largely offsetting the benefit.

To many journalists, commentators, and social media personalities, the conclusion seemed obvious: aspirin no longer worked. That was not, however, what the studies showed.

For people who have already experienced a heart attack, undergone coronary stenting, suffered an ischemic stroke, or developed established atherosclerotic cardiovascular disease, aspirin remains one of the most important drugs in medicine. In these patients, often referred to as secondary prevention populations, the risk of another thrombotic event is sufficiently high that the benefits of aspirin generally outweigh the bleeding risk.[12]

The real debate concerns primary prevention: should a person with no history of cardiovascular disease, or a younger individual hoping to avoid it altogether, take aspirin to prevent a first event? The correct answer is nuanced. Increasingly, the answer depends less on broad population guidelines and more on the biology, genetics, cardiovascular risk, and bleeding risk of the individual.

Large modern trials and meta-analyses show that aspirin can reduce the risk of first heart attacks and ischemic strokes, but the benefit is often modest and frequently offset by an increased risk of major bleeding. In its 2022 update, the U.S. Preventive Services Task Force concluded that adults aged 40-59 with a 10-year cardiovascular risk of at least 10% may derive a small net benefit from low-dose aspirin if they are not at increased bleeding risk, while finding no net benefit for initiating aspirin after age 60 in the general population.[13]

But no one is general. We are all individuals.

One of the most important developments in cardiology has been renewed interest in Lp(a), pronounced *L-P-little-a*. Until recently, Lp(a) was often ignored because many physicians had never measured it and because there were few therapeutic options. Both are changing rapidly.

Lp(a) is similar to LDL "bad cholesterol" but carries an additional protein called apolipoprotein (a). Unlike LDL, which can respond substantially to diet and lifestyle, Lp(a) is predominantly inherited through variants in the *LPA* gene. About 20% of people have Lp(a) levels above the threshold of 50 mg/dL (125 nmol/L). Elevated levels are associated with increased risks of coronary artery dis-

IMAGE SOURCE: JIJOMATHAI VIA ADOBE STOCK

ease, stroke, peripheral vascular disease, and calcific aortic stenosis.[14]

But Lp(a) risk does not begin at an arbitrary threshold. Like blood pressure or LDL cholesterol, the relationship appears continuous. Most guidelines consider levels below 30 mg/dL reassuring and about 25% of people are above this threshold. Several powerful RNA-based drugs, including pelacarsen, olpasiran, and zerlasiran, are now in late-stage clinical development and can lower Lp(a) levels by 80-95%.[14]

In the meantime, however, aspirin has emerged as a surprisingly interesting stopgap.

Several studies suggest that aspirin may provide disproportionate benefit in individuals with elevated Lp(a). The reason is biologically plausible. Lp(a) appears to contribute not only to atherosclerosis but also to thrombosis. If part of a person's cardiovascular risk arises from an increased tendency to form clots, platelet inhibition may be particularly valuable.[15]

This is one reason many preventive cardiologists continue to consider aspirin for selected high-risk patients despite increasingly restrictive guideline recommendations.

This naturally raises the question of testing. Is there a way to determine whether someone should take aspirin?

Not with a single laboratory value, but increasingly with a combination of measurements. Cardiovascular risk estimation remains essential and includes age, blood pressure, Apolipoprotein B, LDL cholesterol, diabetes status, smoking history, family history, and coronary artery calcium scoring. Another important variable is bleeding risk. Prior ulcers, gastrointestinal bleeding, anticoagulant use, advanced age, uncontrolled hypertension, and certain medications can dramatically alter the equation.

Genetics now adds a third dimension. From my perspective, it makes sense to learn your Lp(a) level at least once in your life. It is one of the strongest inherited cardiovascular risk factors known and, unlike many biomarkers, remains relatively stable throughout adulthood.

"Beyond cardiovascular disease prevention, aspirin has also attracted attention in the longevity field. Should aspirin be considered a longevity intervention?"

This is where medicine is heading. Not necessarily toward more medications, but toward better targeting of the ones we already have.

This has practical implications for genetic testing and decision-making. Genetic testing in cardiovascular clinics is increasingly routine and several companies offer testing for inherited variants in the *LPA* gene. Carriers of these variants tend to have markedly elevated Lp(a) levels, nearly double the risk of major cardiovascular events, and in several studies appeared to derive greater benefit from low-dose aspirin therapy.

The biology is compelling: Lp(a) appears to promote both plaque formation and thrombosis, making platelet inhibition especially attractive in this subgroup. Yet most major cardiovascular societies do not currently recommend routine genetic testing to guide aspirin therapy, and many insurers continue to classify these assays as investigational.

Beyond cardiovascular disease prevention, aspirin has also attracted attention in the longevity field. Should aspirin be considered a longevity intervention? Despite being more than a century old, it is one of the few commonly used drugs that has shown lifespan-extending effects across multiple species. Studies in the nematode *Caenorhabditis* elegans have found that aspirin extended lifespan by roughly 20%, increased stress resistance, reduced protein aggregation, and activated longevity pathways involving AMPK and DAF-16/FOXO through mechanisms that overlap with dietary restriction.[16,17]

Similar effects have been reported in fruit flies, where aspirin improved intestinal health and delayed age-related decline.[18,19] Perhaps most surprisingly, the National Institute on Aging's Interventions Testing Program reported that aspirin modestly increased median lifespan by 8% in genetically heterogeneous mice, although the effect was only observed in males.[20]

The translational challenge, of course, is that what works in worms, flies, and even mice does not always work in humans. In fact, most mouse studies fail to translate to humans.[21]

In contrast to the animal data, the ASPREE trial found no longevity benefit in healthy older adults and identified an increased risk of major bleeding.[10] That result does not necessarily mean aspirin has no role in human longevity. It may simply mean that any benefit is confined to specific groups, particularly individuals at elevated cardiovascular or thrombotic risk.

Aspirin does not appear to directly slow indicators of biological aging. It does not reset the epigenome. It does not extend telomeres or kill senescent cells. Yet longevity is ultimately measured in survival. A therapy that reduces the likelihood of a fatal cardiovascular event may meaningfully extend healthy lifespan even if it does not alter the underlying biology of aging itself.

Like many interventions in modern medicine, aspirin appears less likely to be a universal anti-aging drug than a tool whose value depends heavily on biology, genetics, and context. Blood pressure control. Exercise. Sleep. Glucose management. Maintenance of muscle mass. Aspirin belongs in that category. It is not glamorous and it does not promise rejuvenation. But in the right individual it may reduce the probability of one of the most common causes of premature death.

The challenge, and perhaps the lesson aspirin has taught us over the last century, is that medicine increasingly demands precision. The twentieth century searched for universal recommendations. One drug for everyone. One diet for everyone. One answer for everyone. Those days are rapidly disappearing. The future of medicine will depend less on discovering miracle molecules and more on understanding which interventions belong to which people.

Biology keeps reminding us that human beings are not mathematical averages. They are distributions. And subtlety is beyond the scope of most headlines and the interest of many readers.

Aspirin is one of the clearest examples. After all these years, it is not only preventing pain or even heart attacks. It is teaching us how to think about medicine itself.

Consult your physician before starting aspirin therapy or seeking specialized testing for Lp(a) or aspirin responsiveness. For questions about genetic testing related to LPA or other genetic variants, consider speaking with a genetic counselor.

“Like many interventions in modern medicine, aspirin appears less likely to be a universal anti-aging drug than a tool whose value depends heavily on biology, genetics, and context.

IMAGE SOURCE: NIKOLETT EMMERT VIA UNSPLASH

IMAGE SOURCE: AI-GENERATED WITH OPENAI

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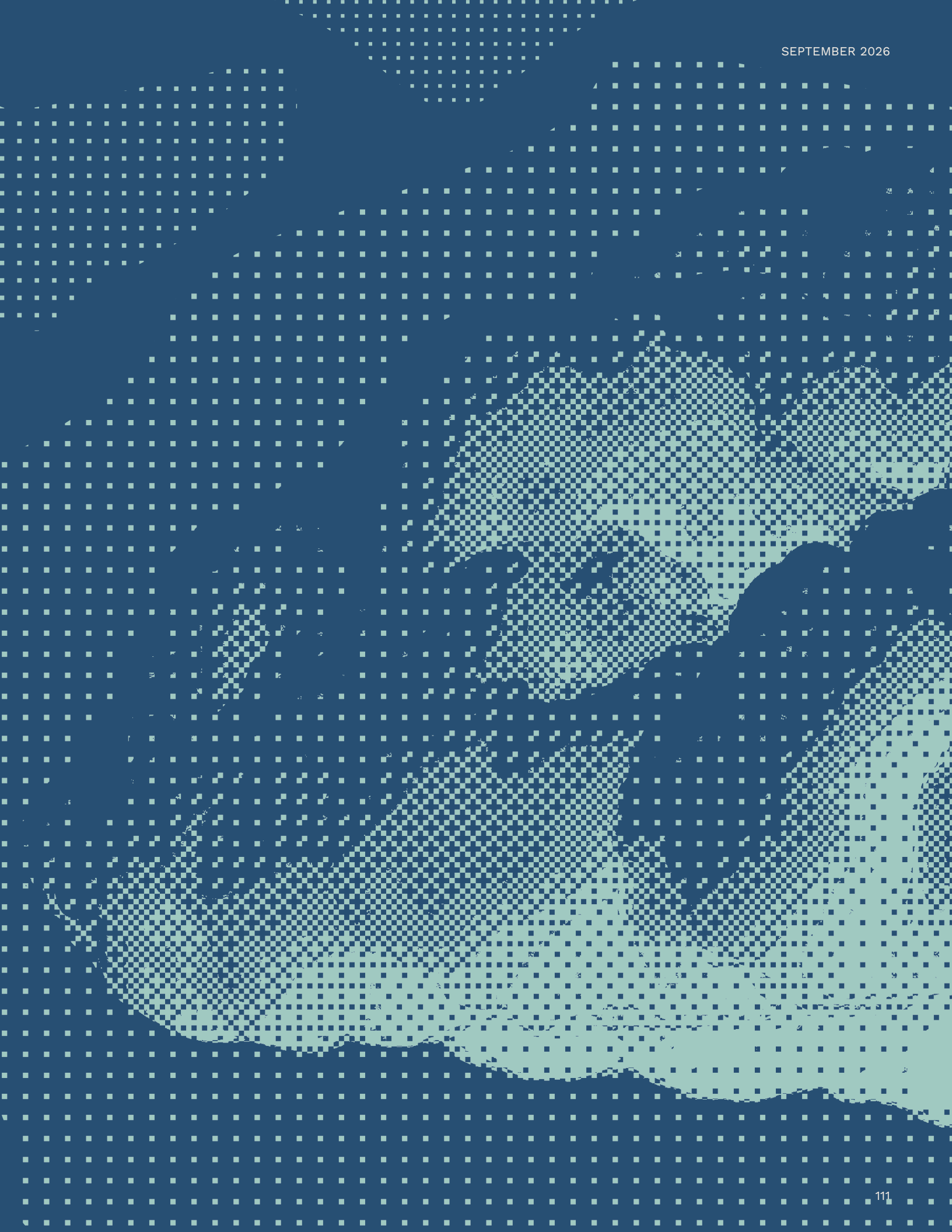
INTERVIEW

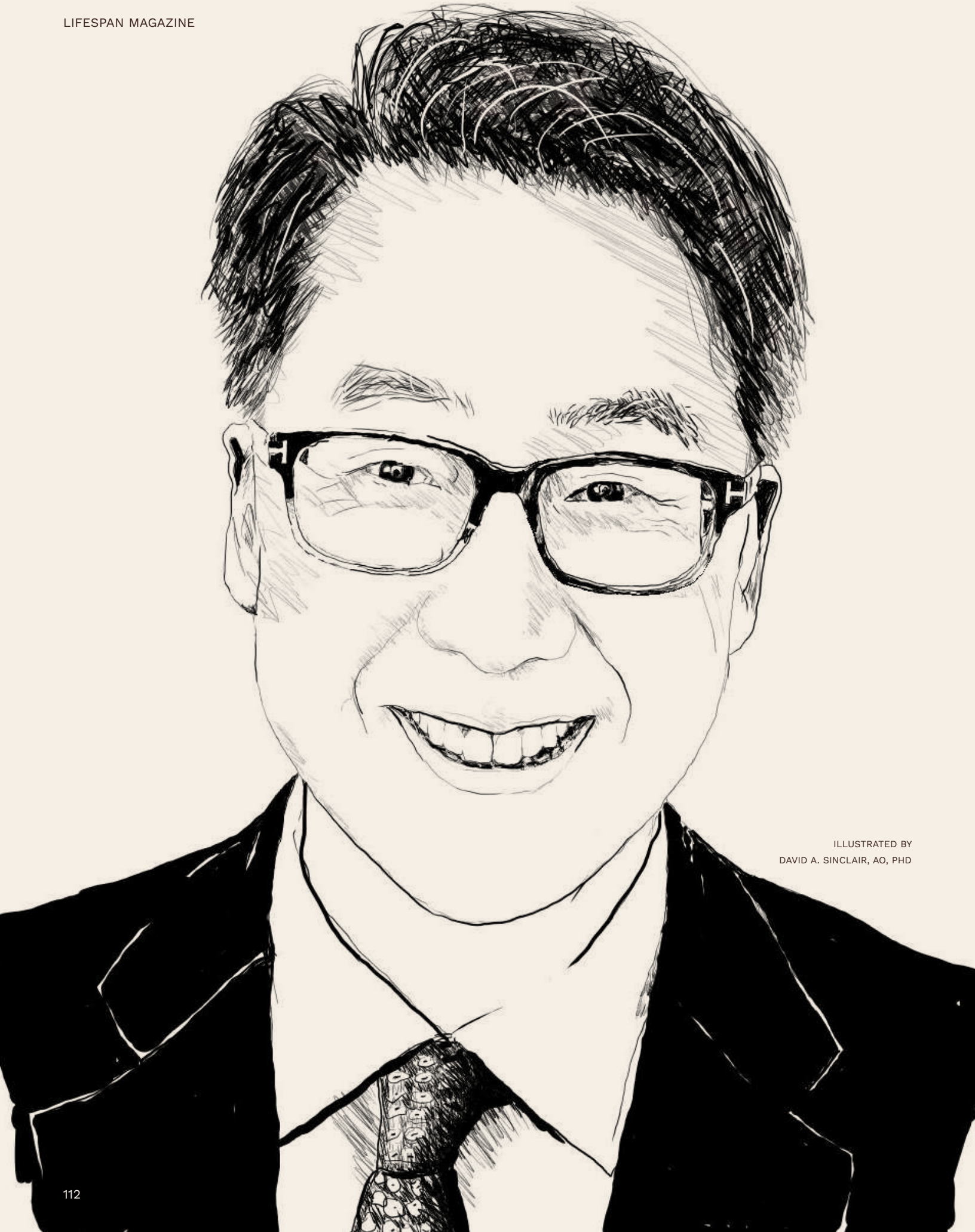
FROM BEDSIDE TO CLOUD:

DR. DAVID RHEW ON USING AI TO HELP US AGE WELL

BY KELLY RICH, MS, CGC, PHD

IMAGE SOURCE: MIDJOURNEY





ILLUSTRATED BY
DAVID A. SINCLAIR, AO, PHD

Dr. David Rhew is a physician, researcher, and technologist who has spent his career trying to make healthcare both smarter and more humane. He is currently the Global Chief Medical Officer at Microsoft, where he leads efforts to harness cloud computing, data, and AI to support clinicians and patients.

A recurring theme in Dr. Rhew's career is using data and technology to make high-quality care more consistent and more accessible, especially for older adults and people managing chronic conditions. In this conversation, we discuss what digital tools can realistically do for healthy aging, how to avoid overwhelming people with in-formation, and what it will take for AI to genuine-ly improve the experience of getting older.

1

Many clinicians feel new technology often adds to their workload instead of reducing it. What would it take for AI and cloud tools to genuinely ease the burden placed on healthcare professionals?

Historically, most healthcare technology was built to digitize manual processes. The electronic health record (EHR) is a good example. Its job was to turn

paper charts into digital ones, but in reality doctors and nurses still have a lot of manual data entry to do. Today, AI can take over many of these repetitive tasks, so clinicians can focus on what matters most: making informed decisions, communicating those decisions effectively, and supporting patients and families throughout their healthcare journey.

Documentation is still one of the most time-consuming parts of a doctor's job. AI "ambient scribe" technology is designed to help with that. During a visit, it listens to the normal conversation between a patient and clinician and automatically turns it into a draft note for the medical record (the EHR). Instead of typing everything themselves, clinicians just review and edit the draft. Studies suggest these tools can cut documentation time by up to 50%, which may also help reduce burnout.

Once those notes are in the system, other AI tools can help clean up the rest of the paperwork. They can check whether the visit has been coded correctly for billing, spot missing information, and flag whether a test or treatment is likely to meet insurance requirements. Taken together, these tools can significantly cut down on administrative work and make the whole system run more smoothly.

2

How do we balance the promise of wearable health trackers with the risk of data overload for the average person?

Before joining Microsoft, I spent six years as Chief Medical Officer at Samsung, where our focus was consumer health. During that time, we observed what I call the "digital health paradox." The people most likely to use wearables (a watch, a ring, a fitness band) were often the least likely to benefit from them. These were the "quantified self" enthusiasts: people who already tracked their steps, sleep, and exercise and were generally healthy. On the other hand, the people who could benefit the most from wearables were often the least likely to use them. Many had multiple ongoing health problems or waited to seek care until their disease had progressed. The challenge was how to engage this second group. What we found was that consumer engagement (getting people involved in their own care) was the critical success factor.

One example was cardiac rehabilitation. Traditionally, after an event like a heart attack, patients attend rehabilitation sessions at a healthcare facility 2-3 times per week for 12 weeks. This program saves lives, but completion rates are low across the country. At Kaiser Permanente, for example, only about 40% of patients completed the program, mainly because of inconvenience, travel requirements, and cost.

When the program was converted into a home-based model supported by wearable technology, completion rates doubled and fewer patients needed to come back to the hospital. Today, home-based cardiac rehabilitation is the preferred alternative to in-person rehabilitation across Kaiser Permanente, and more than 30,000 patients have benefited from it.

3

As an infectious disease physician now working in tech, how do you decide which clinical problems are worth building AI solutions for?

Infectious disease doctors care for both individual patients and entire populations. Sometimes we prescribe antibiotics to treat infections, and other times we do not recommend antibiotics, for example when patients have viral upper respiratory infections. The reason is that unnecessary antibiotic use contributes to antimicrobial resistance (when germs no longer respond to the drugs) making future infections more difficult to treat. This is especially concerning for vulnerable patients, such

as those undergoing cancer treatment or receiving organ transplants.

This perspective shapes how I think about AI. I look for opportunities to improve outcomes at both the individual and population levels.

At the individual level, AI can help alleviate administrative burdens. At the population level, AI can help tackle broader challenges, including expanding access to affordable, high-quality healthcare, reducing the cost of care, and improving chronic disease management. These complex issues are unlikely to be solved by any single tool or app.

Our experience suggests that success requires focusing on three areas:

- Catching health problems earlier and spotting when they are getting worse
- Managing disease effectively despite limited resources
- Empowering consumers and patients to take an active role in their health

AI has the potential to contribute meaningfully in all three areas.

4

Digital health often promises to improve equity and access. Where do you see that really happening today, and where do we still need to improve?

One of the most exciting applications of AI is in reading images of the retina, the light-sensitive layer at the back of the eye. From a single picture, AI can help diagnose disease and spot early warning signs (biomarkers) of several conditions:

- Heart and metabolic diseases, such as diabetic eye disease, cardiovascular disease, high blood pressure, and kidney disease
- Eye diseases, including the four leading causes of blindness: age-related macular degeneration, cataracts, diabetic retinopathy, and glaucoma
- Brain and nerve diseases, such as Alzheimer's disease, multiple sclerosis, and Parkinson's disease

Retinal images can be captured with cameras in eye clinics, primary care offices, retail pharmacies, community health fairs, and potentially even in people's homes. In a pilot program at a rural primary care clinic in East Texas, AI-assisted screening found moderate-to-severe diabetic eye disease in about 20% of patients. In other words, these tools are very good at finding people who need help. The challenge is no longer just detecting advanced disease. The challenge is building systems that can manage the large number of people who now need ongoing care.

One large health system in California has shown that a "virtual reading center" model can work well at scale. In this approach, experts review the eye images remotely, confirm the diagnosis, quickly flag high-risk patients who need to be seen in person, and monitor lower-risk patients who are stable. This is a cost- and time-efficient model that could be adopted nationally and globally.

When combined with AI-enabled retinal screening, models like this can expand access to care, improve outcomes, and help lower healthcare costs, especially for people in rural or underserved communities who might not otherwise see a specialist.

5

As healthcare systems start adopting AI, how should they practically evaluate whether a new tool is trustworthy enough to use in patient care?

As health systems start adopting AI, they need practical ways to decide which tools are safe and trustworthy enough for patient care. Organizations should focus on five key activities:

1. **Know what you're using:**
   Inventory and register all AI models used across the organization, and document them in a standard way.

2. **Test tools on your own data:**
   Validate AI models using local datasets to confirm that performance in your setting matches what is reported.

3. **Keep watching them over time:**
   Continuously monitor deployed models for performance drift (when accuracy changes over time), clinical impact, and return on investment.

4. **Check for bias:**
   Evaluate models for potential bias and assess performance across diverse patient populations to make sure they work reliably for everyone you serve.

5. **Set up clear oversight:**
   Establish a streamlined governance framework that defines who approves AI tools, how they are reviewed, and what happens if problems are discovered.

Even the most mature healthcare organizations will quickly be overwhelmed by the growing number of internally and externally developed AI models. The challenge becomes even greater as organizations begin managing "agentic" AI systems (tools that can take actions, not just make predictions).

To address these concerns, healthcare organizations across the United States and Europe have formed the Trustworthy & Responsible AI Network (TRAIN U.S. and TRAIN Europe). The goal of TRAIN is to help organizations govern and manage AI in a cost-, time-, and resource-efficient manner. TRAIN uses technology and a "learning health network" approach, meaning that organizations share testing results, monitoring data, and implementation lessons with others who are evaluating the same AI models

6

Looking five to ten years ahead, what is one realistic way you hope AI and cloud technology will change the everyday experience of being a patient?

Consumer and patient engagement is strongly associated with better health outcomes and lower healthcare costs. Engagement involves understanding what's going on with your health, asking questions, speaking up when something doesn't seem right, following treatment plans, and navigating an increasingly complex healthcare system.

AI, when applied to an individual's health information in a secure and privacy-preserving way, has the potential to act like a smart guide. It can help people make sense of their records, prepare for appointments, remember medications, and know when they should reach out for help, so they can take a more active role in their own care.

Importantly, this is not just a vision for five to ten years from now. It is beginning to happen today. One example is Microsoft Copilot Health, an AI assistant designed to help people understand their health information and navigate the healthcare system.

7

When you think about the future of aging and longevity research, what are you personally most excited about? What worries you?

What if we could not only slow aging, but potentially reverse aspects of it? The idea may sound improbable today, but so once did the prospect of putting a person on the moon.

At the same time, I worry about unintended consequences. I sometimes think about Indiana Jones and the Last Crusade, where several characters seek the Holy Grail in pursuit of extended life. Yet those who chose unwisely experienced the exact opposite outcome.

The same caution applies to longevity science. Interventions designed to extend lifespan or healthspan may produce unexpected side effects. For that reason, all potential therapies should undergo rigorous safety testing and clinical evaluation. We must also carefully consider the ethical implications of these treatments and how they should be used.

What's coming next month

Turning Back Time

How Climate Change Rewrites the Biology of Aging

What Can We Learn About Aging from Astronauts?

What Your Face Knows About Your Health

Is Aging a Disease? A Written Debate

How a 117-Year-Old Bent the Rules of Aging

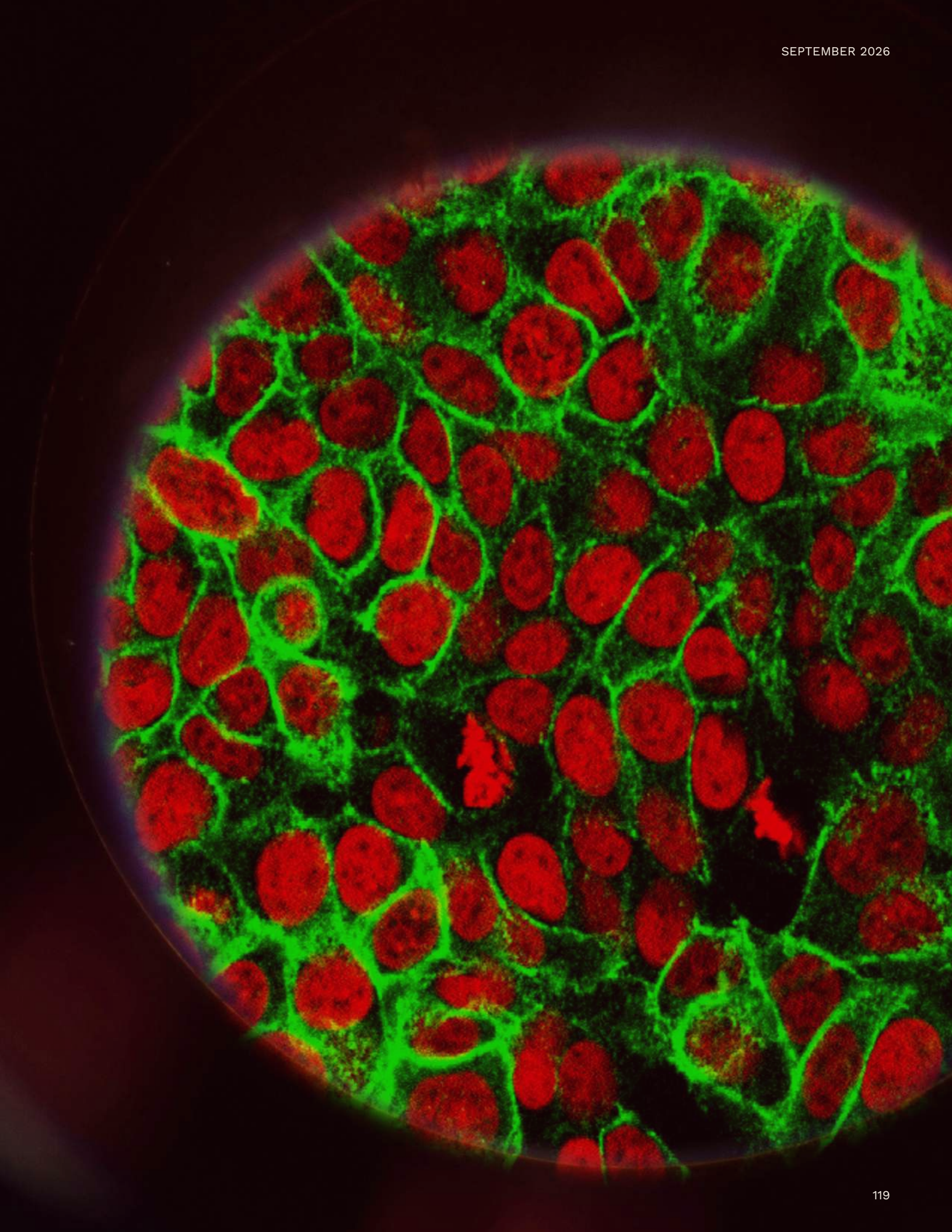
Longevity Fixation Syndrome: When Healthy Habits Go Too Far

Living Longer, But Not Better?

Short Sleep, Long Sleep and the Sweet Spot in Between

Can Rejuvenation Help Us Grow New Body Parts?

IMAGE SOURCE: NATIONAL CANCER INSTITUTE, 2024 VIA UNSPLASH



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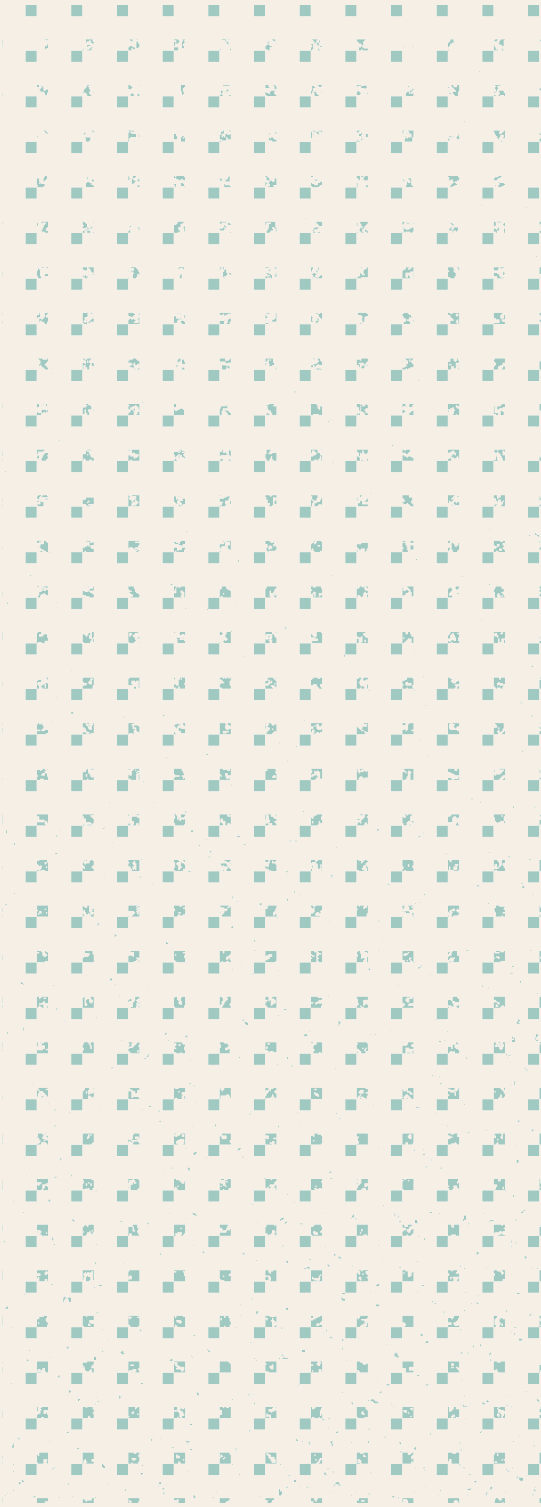

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