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Revisiting Medicine 3.0

Improving Healthspan And Lifespan To Live A Rich, Long Life

The Tools I Rely On To Translate Cutting-Edge Science Into Daily Practice

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Porter & Co.

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In the summer of 1955, a 65-year-old man stood on the dusty shoulder of a Kentucky highway, staring at the shuttered roadside restaurant he had spent the last decade trying to build. A new interstate had diverted every driver, every customer, every dollar away from his restaurant.

His business was gone. So was his income. And aside from a monthly $105 Social Security check, so was his financial future.

Most people at that age would have accepted their fate – quietly, maybe bitterly, slipping into the gray anonymity of retirement. But Harland Sanders did something different. He put on a white suit, packed a pressure cooker into the trunk of his Oldsmobile, and set out across the country to sell fried-chicken franchises door to door. He slept in his car. He was turned down more than 1,000 times. But he kept going.

Eight years later, at age 73, "Colonel" Sander sold Kentucky Fried Chicken ("KFC") for $2 million – over $20 million in today's dollars. He retained lifetime royalties and became one of the most recognizable entrepreneurs on the planet. Today, KFC operates more than 25,000 restaurants worldwide.

Society tells us in countless ways that life's greatest acts don't happen in our seventh decade. Colonel Sanders refused to believe it.

His story is more than an entrepreneurial inspiration. It's a parable about human potential, and what becomes possible when our healthspan – the number of years we remain strong, sharp, vibrant, and functional – is extended deep into later life. Sanders succeeded not because he lived longer, but because at 65 he still had enough energy, resilience, and capacity left to mount a third act.

Modern medicine has long focused on lifespan – adding years to life. But if we want to unlock the possibility of a "second curve," a late-life reinvention, a Sanders-like third act, we need something equally valuable: adding life to years.

This month's *Tech Frontiers* differs from most issues. We will not be focusing on a new stock recommendation. Instead, we'll revisit a theme I first wrote about in our **April 2024 issue** – "Medicine 3.0: Investing In Ways To Live Longer." I borrow the term *Medicine 3.0* from my friend Dr. Peter Attia, the Stanford Medical School-trained physician and longevity expert who coined the designation in his magnificent book *Outlive*.

Medicine 3.0 refers to the next-generation practices that *patients* need to adopt, drawing on cutting-edge science that's not yet widely permeated the medical mainstream, if we wish to maximize our healthspan as well as our lifespan. By being proactive, informed, and by taking concrete action, we can add *both* years to our lives, and life to our years.

I've organized our discussion in this issue into seven categories. Each focuses on a different aspect of Medicine 3.0 that impacts healthspan as well as lifespan. We'll examine:

1. Sleep: The Most Potent – And Overlooked – Longevity Drug
2. Cardiovascular Disease: The Preventable Killer
3. Harnessing Early Detection To Conquer Cancer
4. Protecting Our Brains From Neurodegenerative Disease
5. Avoiding The Silent Threat Of Metabolic Syndrome
6. Japan's Longevity Lessons
7. Relationships, Community, And Belonging – The Most Underrated Longevity Drugs

As subscribers who have read Dr. Attia's *Outlive* – or our April 2024 issue – may recall, some of these categories focus on what Attia calls the "Four Horsemen": cardiovascular disease, cancer, neurodegenerative disease (such as Alzheimer's), and metabolic illnesses (such as diabetes), which are the four biggest killers of Americans over age 40. Other categories focus on important domains that cut across these diseases and affect all aspects of our health.

In each category of our discussion, my aim is to share both cutting-edge science and practical advice. For that reason, where it's applicable, I'll share how I myself am seeking to translate Medicine 3.0 insights into action, including the specific tools I'm using. As a 53-year-old dad of three kids – the eldest of which is only 16 – I'm intensely motivated to maximize my lifespan and healthspan. My aim is not only to "make it" to meet my grandkids – but to have enough left in the tank to be an active grandparent.

Over the two years that I've written *Tech Frontiers* (and its predecessor, *Biotech Frontiers*), many subscribers have been in touch to thank me for the success of our investment recommendations, and to share the ways in which the gains they've made in our portfolio holdings have been life-changing for them. I'm beyond grateful for this kind feedback.

But the single most meaningful exchange I've had with a subscriber happened at the Porter & Co. Annual Conference in 2024. A young man, barely in his 40s, approached after I spoke from the stage. He explained that he had read our April 2024 issue on Medicine 3.0 and, after reading it, signed up for a Prenuvo scan – the whole-body MRI scan that I discuss again in this issue. He wasn't feeling ill or unwell when he signed up for the scan. He was simply seeking to implement the recommendations we wrote about.

The scan discovered an asymptomatic malignant tumor on his kidney. Fortunately he caught this before the cancer had metastasized – and as a result, he was able to have it surgically removed. His prognosis is excellent. He should be able to live a full, long life. But had he not caught the cancer at this stage – well before any symptoms appeared – the outcome would likely have been very different. He credits the Prenuvo scan with saving his life.

The recommendations we write about this month won't, of course, have such a dramatic impact for most of us. But – every bit as much as the financial investments we ordinarily cover, and to which we'll return next month – I hope these recommended investments in your health compound over years to give you a longer, richer, and better life.

Let's begin...

1. Sleep: The Most Potent – And Overlooked – Longevity Drug

In a world obsessed with diets, training routines, and precision diagnostics, the most powerful longevity medicine remains free, ancient, and universally available: sleep. That's right, if there's a single intervention that delivers broad, compounding returns for healthspan and lifespan, it's high-quality sleep. As University Of California, Berkeley, neuroscientist Dr. Matthew Walker argues in his important book, *Why We Sleep*, a good night's rest isn't merely one pillar of wellbeing – it's a bedrock for everything else. Deep, consistent eight-hour sleep protects the cardiovascular system, strengthens the immune system's cancer surveillance, wards off metabolic dysfunction, preserves cognitive capacity, and triggers the cellular repair processes that slow biological aging.

The science behind sleep's contribution to longevity is staggering. Just one night of poor slumber can raise blood pressure, impair insulin sensitivity, and suppress the body's natural-killer immune cells – those cells responsible for eliminating emerging cancer lines – by up to 70%. Chronic under-sleeping accelerates amyloid and tau

accumulation in the brain, driving neurodegeneration and increasing Alzheimer's risk. Poor sleep inflames the cardiovascular system: heart attack rates spike in the U.S. the day after daylight saving time steals one hour. And sleep is the master metabolic regulator – governing cortisol, leptin, ghrelin (the hunger hormone), insulin, and growth hormones – meaning that chronic sleep impairment pushes the body into a hormonal profile indistinguishable from accelerated aging. Epidemiological studies converge on a bracing truth: routinely sleeping less than seven hours a night dramatically shortens lifespan.

The flip side is just as powerful. High-quality, regular sleep is a force multiplier that amplifies every other positive health intervention. It enhances the benefits of exercise, improves glycemic control from dietary choices, preserves cognitive performance, enhances emotional resilience, and strengthens the immune system's ability to detect and destroy malignant cells. Deep sleep functions as a nightly neurological detox, flushing metabolic waste and preventing the slow accumulation of toxins that erode memory and executive function. REM sleep, when the brain is active and dreams transpire, recalibrates the brain's emotional circuits and consolidates learning – both crucial to long-term wellbeing. It's no exaggeration to say sleep is the simplest, most accessible, and most under-leveraged longevity intervention we have.

I use two pieces of technology to help translate this science into practical benefits.

1. An **Oura Ring** is a simple, elegant device that's so unobtrusive I often forget I'm wearing it. Placed on the finger, the ring provides continuous, accurate measurement of my sleep duration and quality, turning each night into actionable data that I can read in seconds on my iPhone the next day. If you want to improve something, you've first got to measure it – and an Oura Ring empowers me to do that for sleep.

2. I also use an **Eight Sleep Pod**: a "smart tech" cooling system that fits over any mattress and lets you find and calibrate the temperature at which you sleep best. In a wonderful bit of technological magic, this system enables you to precisely adjust the temperature on each side of a bed – so if your partner sleeps better when warm and you sleep better when cool, the Eight Sleep coverlet allows you to precisely set the optimal temperature for each of you.

Together, these two pieces of technology – an Oura Ring and an Eight Sleep Pod – offer simple, high-impact ways to improve the single most powerful longevity habit we all can invest in.

2. Cardiovascular Disease: The Most Preventable Killer

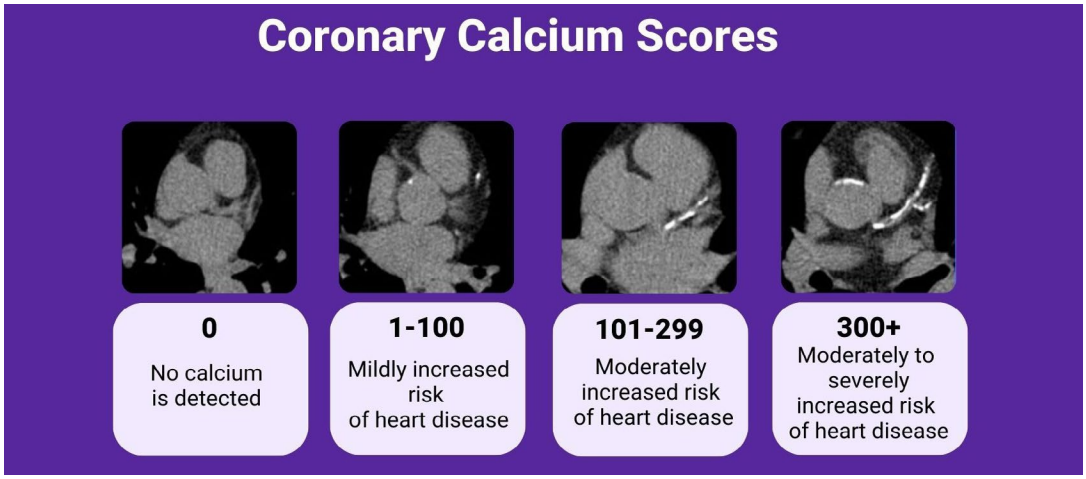
Cardiovascular disease ("CVD") remains the leading cause of death in the United States, claiming more lives each year than all forms of cancer combined. But for individuals willing to take a proactive approach to their health, it's also the most preventable chronic illness. Centuries of study have enabled us to make only moderate progress in understanding how to prevent cancer, and even less progress with Alzheimer's. But we know how to prevent cardiovascular disease.

As Dr. Attia emphasizes in *Outlive*, while CVD strikes many victims in the form of a sudden catastrophe – a heart attack or stroke – it's actually a disease that unfolds slowly and silently over decades before it reaches its end state. The tragedy is that most Americans are tracking the wrong markers, relying on outdated proxies such as total cholesterol or LDL-C, while the real culprits driving CVD remain unmeasured and untreated. We need an updated view of what to look for as well as a more proactive approach once we identify early-warning signs.

The first step lies in measuring the right biomarkers – those that accurately predict CVD risk. The single most important one is **ApoB**, the protein "container" that carries all atherogenic lipoproteins capable of infiltrating the arterial wall. Every ApoB particle – whether an LDL particle, VLDL particle, or lipoprotein(a) particle – has the potential to enter a blood vessel's lining and trigger plaque formation. LDL-C, the marker most doctors measure, is merely the cholesterol *content* inside these ApoB particles, not the particle count itself, making LDL-C a poor surrogate. An individual with "normal" LDL-C may still have an elevated number of ApoB particles and therefore high cardiovascular risk.

Other critical CVD-risk biomarkers include **Lp(a)** (genetically determined and highly atherogenic), **hs-CRP** (a measure of vascular inflammation), **fasting insulin**, **triglycerides**, and HbA1c. Together, these biomarkers provide a far clearer view of metabolic and vascular health than the crude lipid panels most Americans rely on. I encourage every *Tech Frontiers* reader to insist on having these biomarkers measured in their next blood panel.

Beyond regularly measuring the right biomarkers, a one-time coronary CT angiogram – or at minimum a coronary artery calcium ("CAC") score – is one of the most powerful early-warning tools available. These scans quantify calcified and non-calcified plaque, allowing patients to "see" the true state of their arteries. A CAC score of zero is dramatically protective, while a high score (300 or above) demands aggressive action, while 1,000 or above puts you at high-risk. As Dr. Attia notes, this is the difference between guessing and knowing one's true risk of a heart attack or stroke.



Most health insurers will not pay for a CT angiogram or CAC score diagnostic unless a cardiologist prescribes one as a follow-up to other worrisome symptoms. This approach – while understandable as a cost-containment measure for insurers – does not serve patients well. It's tantamount to waiting until CVD has advanced before deploying the most sophisticated diagnostics. For this reason, I think it's well worth it for subscribers to pay out of pocket for a one-time CT angiogram or CAC score even with no CVD symptoms at all, simply to obtain an accurate baseline of their true cardiovascular disease risk.

If either our biomarkers or our CAC score signals any elevated CVD risk, a deep and effective toolbox exists with which to mitigate it. However, doing so requires aggressive intervention with the help of a physician willing to look past the outdated paradigm that still holds sway in mainstream cardiac care. For reasons I'll share at greater length in a separate issue of *Tech Frontiers*, I have considerable skepticism about the net benefits of statins (such as Lipitor) – the "first line" medicines that most physicians prescribe to manage elevated cholesterol.

Following Dr. Attia, I am a far bigger fan of what are considered the second-line therapies – **PCSK9 inhibitors and Bempedoic acid (Nexletol)**. These medicines can reduce ApoB 50% to 60% beyond what statins alone can achieve. In the fullness of time, I think the evidence will also show they have a much more benign impact on most patients' metabolic profile, which impacts healthspan as well as longevity. So I would exhort readers who are either taking statins or need to proactively manage their CVD risk based on test results to shop around for a physician who is sympathetic to the case against statins – and willing to prescribe PCSK inhibitors and/or Bempedoic acid instead.

Dr. Attia likes to say that while cardiovascular disease is America's #1 killer, it shouldn't even be in the top 10. *Tech Frontiers* readers have the ability to dramatically reduce their risk from CVD. But doing so requires taking proactive steps to measure the right markers with the right tests, and then – if necessary – aggressively pursue the right interventions.

3. Harnessing Early Detection To Conquer Cancer

After cardiovascular disease, cancer is the second leading cause of death in America, responsible for more than 600,000 deaths each year. But unlike CVD, where the causal chain is well-understood and the tools of prevention are powerful, cancer remains a far more elusive adversary. We cannot yet reliably prevent – or cure – most cancers. What we can do is dramatically improve our chances of surviving them. And the key to doing so is simple, fact-based, and too often ignored: catch cancer early, before it spreads.

Across nearly every major solid tumor category, the survival gap between early-stage and late-stage cancer is arresting: In stage I or stage II, when cancer remains localized, five-year survival typically ranges from 70% to 95%, depending on tumor type – and in many cancers, early treatment offers a real possibility of cure. But once cancer reaches stage III or stage IV, when it has invaded lymph nodes or metastasized to distant organs, five-year survival often falls into the teens or single digits.

A few examples make the point: For non–small-cell lung cancer, stage I patients have a 61% five-year survival, while stage IV patients face just 7%. For cervical cancer, stage I implies ~85% five-year survival, versus ~7% in stage IV. Thyroid cancer shows a similar pattern: near 100% survival in early stages, dropping to 50% once the disease spreads. Across tumor types, the pattern is consistent: Cancer caught early behaves like a treatable disease. Cancer caught late behaves like a terminal one.

This leads to a crucial, Medicine 3.0 insight: When it comes to cancer, early detection is not merely beneficial – it's everything. Unlike heart disease, where lowering ApoB or blood pressure can slow or reverse pathology, cancer does not give us many second chances. This means that for individuals serious about maximizing longevity and healthspan, the name of the game when it comes to fighting cancer is reliable, regular surveillance – the kind that finds a cancer while it's still small, localized, and treatable.

Two technologies represent the frontier of such surveillance: **whole-body MRI** and, for women, next-generation **breast imaging**.

Preventative whole-body MRI, innovated by companies such as Prenuvo, offers a radiation-free, contrast-free, non-invasive scan capable of detecting tumors smaller than a centimeter across the entire body. Prenuvo's MRI protocols are optimized for early cancer detection, scanning for masses in the brain, neck, chest, abdomen, pelvis, spine, and extremities in a single session that typically takes less than an hour. Patients can choose to wear goggles that allow them to watch Netflix comfortably during a scan, making the whole experience feel almost like an hour spent taking in an episode of a favorite streaming series. Unlike CT or PET imaging, MRI does not expose patients to cumulative radiation – which means a regular MRI offers a safe, repeatable way to catch cancers long before they cause symptoms.

Now eight years old, Prenuvo has amassed data on thousands of patients who have come in for scans. This data indicates Prenuvo detects cancer in about one out of every 20 patients. Impressively, 95% of these cancer cases are caught at stage I. Signing up for a Prenuvo scan does not require a prescription. The company now features 17 centers across North America, with plans to open 15 more. At $2,000 to $2,500 per scan, the technology isn't cheap, but it's also not prohibitively expensive. I do a Prenuvo scan annually and regard it as among the very best investments in my health (and peace of mind) available. *Full disclosure*: I am a small investor in Prenuvo – an investment I made after doing my first Prenuvo scan and becoming a huge believer in the company's approach to proactive cancer detection.

For women, augmenting Prenuvo's whole-body approach with advanced breast surveillance is equally critical. Nearly half of all women have dense breast tissue, which makes standard mammography (and even MRI) far less effective at detecting early tumors. **Eve Wellness**, a leader in state-of-the-art automated breast ultrasound coupled with AI-enhanced imaging, offers a radiation-free, more sensitive alternative for women with dense breasts. Its technology improves detection of small, early-stage lesions that mammography frequently misses – precisely the cancers that are most curable if found early. For the men reading this issue, don't ignore this paragraph. Instead, urge your wife or girlfriend to embrace regular breast ultrasounds or, better yet, sign her up yourself. Consider it a wise investment in both of your healthspans.

Together, whole-body MRI and advanced ultrasound represent a new paradigm in cancer risk management, shifting us from reactive medicine ("diagnose it after symptoms appear") to proactive, continuous surveillance that catches cancer at the only time it's reliably beatable: early. I encourage *Tech Frontiers* readers to take advantage of these game-changing technologies.

4. Protecting Our Brains From Neurodegenerative Disease: Taking Action Today, Keeping A Vigilant Eye On Tomorrow

Of Dr. Attia's "Four Horsemen," neurodegenerative disease – especially Alzheimer's – remains the most enigmatic and formidable. We understand far less about its underlying mechanisms than we do for cardiovascular disease, cancer, or metabolic illnesses such as diabetes. And despite decades of scientific effort and tens of billions of dollars in research spending, today's Food And Drug Administration ("FDA")-approved Alzheimer's therapies are very far from cures. Even those marketed as "slowing progression" deliver modest, ambiguous results. Yet this state of play does not leave us powerless. A Medicine 3.0 approach to brain health offers us three levers:

1. understand our genetic risk
2. double down on the habits that move the needle
3. keep a close eye on emerging RNA-based therapies that may, for the first time, meaningfully shift the trajectory of neurodegenerative diseases during our lifetimes

Lever #1: Know Our Genetic Risk – Especially Our APOE Status

Among all known genetic determinants of Alzheimer's, the **APOE gene** has by far the largest effect. Each of us carries two APOE alleles – ε2, ε3, or ε4 – and the combinations create dramatically different lifetime risk profiles for neurodegenerative illness. A single ε4 allele increases Alzheimer's risk two- to three-fold. Meanwhile, two ε4 alleles raise that risk *eight- to 14-fold* versus the baseline. By contrast, the ε2 allele appears protective.

Genetic testing for APOE is inexpensive, simple, and actionable. It does not directly predict, much less diagnose, Alzheimer's disease. Instead, like a CT angiogram or CAC score for cardiovascular maladies, it calibrates risk and helps inform the urgency with which we need to pay attention to this third "horseman." If you carry APOE ε4 – especially if you're a double carrier – the imperative to **optimize sleep, metabolic health, cardiovascular markers, and inflammation** increases. As with ApoB in heart disease, calibrating your risk profile empowers you to take action.

Lever #2: Invest In The Simple Prevention Habits That Matter

While genetics loads the gun, lifestyle pulls the trigger. The convergent evidence on long-term cognitive preservation points toward a simple but helpful playbook of beneficial habits:

- **Deep, consistent sleep**, which clears metabolic waste, restores immune surveillance, and prevents amyloid and tau accumulation
- **Exercise**, both aerobic and strength-based, improves vascular integrity, glucose control, neurotrophic signaling, and inflammation

- **Maintaining metabolic health**, emphasizing insulin sensitivity and low inflammatory load
- **Not ignoring oral and dental health**, because chronic gum disease correlates with elevated dementia risk, a correlation that is coming to make more sense given emerging theories about the etiology of neurodegenerative illnesses
- **Prioritizing emotional and environmental hygiene**, reducing chronic stress, sedentariness, and other slow-drip insults to cognitive resilience

None of this is glamorous – but, especially for APOE ε4 carriers, these habits should be non-negotiable levers.

Lever #3: The Future Promise Of RNA-Based Therapeutics

Past times I have written about Medicine 3.0 – in our April 2024 issue and for literally decades before then – I've been a pessimist about the likelihood of developing effective cures for serious neurodegenerative diseases such as Alzheimer's. Indeed, in our April 2024 issue, I mentioned my old college and grad-school friend "Dr. M.," one of the preeminent physicians/scientists of his generation, who warned me when we were in our 20s (and he was at Harvard Medical School): "Erez, never invest in a company developing an Alzheimer's cure. It's a biotech graveyard." For three decades, he's been right.

Today, for the first time ever, I'm cautiously optimistic that we may yet see therapies that "bend the curve" of this terrible disease category in our lifetimes. The reason is the promise of siRNA therapeutics, a new medical modality that *Tech Frontiers* readers already know well from our work on the Era of Genetic Medicines and our recommendation of **Alnylam Pharmaceuticals (Nasdaq: ALNY)**. RNA interference programs suggest a new, upstream strategy for attacking neurodegenerative illness: silencing the genes that produce pathogenic proteins in the brain in the first place.

In most neurodegenerative diseases – and Alzheimer's in particular – the pathology begins years before symptoms appear – driven by the slow, relentless accumulation of aberrant proteins inside the brain. In Alzheimer's, two proteins dominate the landscape: beta-amyloid, which forms sticky extracellular plaques, and tau, which misfolds into toxic tangles inside neurons. Still others, such as BACE1 (an enzyme that generates amyloid fragments), APOE4 (which impairs protein clearance and accelerates inflammation), and a host of inflammatory mediators, contribute to a vicious cycle of neuronal stress, synaptic loss, and ultimately cell death. For decades, drug development focused downstream – trying to clear plaques once they were already present, or to dampen inflammation once it was already raging. This approach is the medical equivalent of mopping the floor while the faucet is still running.

It also highlights why siRNA represents such a promising, fundamentally different approach. Instead of attempting to remove toxic proteins after they accumulate, RNA interference seeks to silence the genes that manufacture them in the first place. siRNA acts like a molecular off switch, binding to the messenger RNA that encodes proteins such as APP, BACE1, tau, and even APOE4, and marking those transcripts for destruction before they can be translated. Early clinical signals – including Alnylam's ALN-APP program and Regeneron's RNAi work – have shown that targeted protein suppression in the central nervous system is biologically achievable, dose-dependent, and durable. In principle, these siRNA therapies could move intervention upstream of plaques, tangles, and inflammation – attacking the root of the process rather than its consequences.

Significant challenges remain: Delivering siRNA safely and efficiently across the blood-brain barrier is non-trivial, and we still need long-term human data to demonstrate meaningful cognitive preservation. But for the first time in decades, the scientific arrow is pointing toward a modality that could plausibly alter the natural history of Alzheimer's rather than merely slow its decline. It's early – but it's real.

Protecting our brain health calls on us to adopt a disciplined, three-step strategy:

1. learn our genetic risk

2. live in a way that reduces it given the simple tools available

3. keep a close eye on emerging modalities in genetic medicine that may finally rewrite the script

Neurodegenerative disease may be today's most stubborn horseman – but with a proactive mindset and the fast pace at which siRNA will evolve over the coming decade, it may not remain so over our lifetimes.

5. Avoiding The Silent Threat Of Metabolic Syndrome – Getting Our Metabolic House In Order

If sleep is the most potent longevity drug and cardiovascular disease the most preventable killer, metabolic syndrome is the silent accelerant that makes every one of the Four Horsemen more dangerous. Most of us likely underestimate how close we are to this condition. While roughly 38 million Americans are formally diagnosed with diabetes, 100 million to 120 million more – nearly half the U.S. adult population! – meet several criteria for *pre-diabetes or metabolic syndrome*, the precursor state that almost always precedes Type 2 diabetes. As Dr. Attia emphasizes in *Outlive*, metabolic syndrome is not a niche problem, but instead the metabolic default of modern life, a slow drift toward insulin resistance that quietly raises the risk of cardiovascular disease, cancer, and neurodegeneration long before blood sugar crosses into the diabetic zone.

The first step in taking our metabolic syndrome risk seriously is to identify it. Diagnosis of metabolic syndrome rests on five specific, measurable criteria. Having three out of five of these leads to an affirmative diagnosis. But Dr. Attia is also unequivocal: Even two of these markers trending in the wrong direction should be a spur to aggressive action.

The five diagnostic criteria are:

1. **High blood pressure** – generally ≥130/85 mmHg, signaling vascular rigidity and endothelial stress
2. **High triglycerides** – ≥150 mg/dL, suggesting poor lipid metabolism and metabolic inflexibility
3. **Low HDL cholesterol** – <40 mg/dL in men or <50 mg/dL in women, reflecting impaired reverse cholesterol transport
4. **Elevated waist circumference** – waist circumference >40 inches in men or >35 inches in women, indicating excess visceral fat
5. **Elevated fasting blood glucose** – typically ≥100 mg/dL, a red flag for impaired glucose regulation

Why does this constellation matter? Metabolic syndrome, at its core, is another name for insulin resistance – the condition in which cells grow numb to insulin's signals, forcing the pancreas to pump out more insulin to maintain normal glucose levels. And insulin resistance is not benign at all – it is one of the most destructive biological states a human can inhabit.

Dr. Attia cites a series of sobering statistics that should re-calibrate our sense of urgency. Insulin resistance is associated with:

- 12x increase in cancer risk
- 6x increase in CVD risk
- 5x increase in Alzheimer's risk

In other words, insulin resistance and metabolic dysfunction are a force multiplier for every one of the Four Horsemen – a molecular accelerant that makes each disease category more likely, more aggressive, and more lethal.

The good news is that metabolic syndrome is also profoundly reversible. If your diagnostic check-up indicates you're drifting toward it – or are already there – a Medicine 3.0 course-correction can shift your trajectory within months:

- **Prioritize muscle and movement:** Skeletal muscle is the body's largest glucose sink. Resistance training and Zone 2 aerobic work are the most powerful tools we have for enhancing insulin sensitivity.
- **Reduce refined carbohydrates and ultra-processed foods:** Lowering glucose spikes reduces insulin load. Favor whole foods, high-quality proteins, healthy fats, and fiber-rich vegetables.

- **Use continuous glucose monitoring ("CGM") or periodic blood panels:** What gets measured gets managed. CGMs provide immediate feedback about your personal glycemic response.
- **Maintain a healthy waist circumference:** Visceral fat is metabolically active and inflammatory. Even modest reductions yield outsized improvements in insulin signaling. We'll discuss strategies to shrink visceral fat in the next section – Lessons From Japan.
- **Sleep deeply:** Sleep deprivation independently worsens insulin resistance – making it a metabolic toxin. Avidly pursue the sleep strategies we've covered.
- **Consider pharmacologic assistance when appropriate:** Metformin, GLP-1 agonists, or SGLT2 inhibitors can meaningfully help those struggling to restore metabolic health through lifestyle alone.

The bottom line: metabolic integrity is foundational to healthspan and lifespan. Without it, every other intervention – sleep, cancer surveillance, cardiovascular biomarkers – operates on compromised terrain. Getting our metabolic house in order is one of the most important steps we can take to help our health compound positively.

6. Japan's Longevity Lessons: Stay Active, Eat Less, Live Longer

Among wealthy nations, Japan stands alone. The average Japanese adult lives roughly a decade longer – and, crucially, a decade *healthier* – than the average American. Their obesity rate is one-tenth that of the U.S. (4% versus 40%). Their rates of cardiovascular disease, diabetes, and neurodegenerative illness are markedly lower. And they boast the highest average life expectancy in the world.

This raises a simple, provocative question: Why?

Japan does not have genetically superior citizens. The Japanese do not take more supplements, have radically different healthcare systems, or practice magic. Instead, as decades of public-health and behavioral research make clear, the Japanese longevity advantage stems from two intertwined cultural commitments: **they move more, and they eat less**. These habits – mundane, unglamorous, profoundly powerful – offer longevity lessons that Americans can adopt immediately and at essentially no cost.

First, let's touch on the Japanese ethos of daily movement.

Unlike in the U.S., where sedentary lifestyles dominate, the Japanese weave physical activity into the fabric of everyday life. Morning group calisthenics are common. Schools, workplaces, and communities normalize regular stretching and mobility work. Their average **daily step count** is nearly double that of the United States. They walk to transit, walk during breaks, walk to dinner, walk home. Movement is not exercise in the American sense – something to be scheduled and endured. Instead, it's ambient, automatic, and culturally reinforced.

This ethos aligns perfectly with the guidance in Dr. Attia's *Outlive* and in our Medicine 3.0 framework: Moderate (or Zone 2) aerobic exercise, daily low-level movement, and resistance training are cornerstones of long-term metabolic and cardiovascular health. Chronic sedentariness is one of the most toxic habits in modern American life – but also one of the easiest to fix.

I recently adopted my own simple target to ward this inactivity off: **taking 8,000 steps a day**, which I track easily – indeed automatically – with the same Oura Ring that helps measure my sleep. I did not choose this threshold randomly: 8,000 steps per day is the level at which, data shows, the curve of mortality risk sharply declines.

Let's now touch on the other half of Japan's longevity advantage: their relationship with food.

Japan's cultural norm of *hara hachi bu* – eat until you are 80% full – is perhaps the single most powerful dietary practice ever studied. Instead of the American pattern of eating until stuffed (or until the plate is empty), the Japanese stop when they are *satisfied*, not stretched. This practice prevents the chronic caloric overload that drives obesity, insulin resistance, vascular inflammation, and cognitive decline.

Caloric restriction – within reason – is one of the most reliable levers for extending lifespan across species. Here, too, I've translated Japan's approach into an actionable, numerical target for myself: I aim to consume roughly 10% fewer calories daily than U.S. dietary guidelines recommend for my weight and age. This approach doesn't feel like a "diet" to me, and I am not seeking to hit any specific target weight. Instead, I'm pursuing a gentle, persistent underconsumption that doesn't leave me chronically hungry but that also avoids the stuffed sensation we Americans know all too well.

Together, Japan's cornerstone habits around activity and eating form a powerful, low-tech longevity protocol:

- Move frequently
- Train deliberately
- Walk everywhere you can
- Eat a little less than you think you need
- Favor whole foods
- Stop before you're full

These practices significantly reduce the risk of being afflicted with any one of the Four Horsemen – cardiovascular disease, cancer, neurodegeneration, and metabolic illness – without requiring genetic insight, pharmaceutical intervention, or advanced diagnostics. Japan has already run the experiment for us. The results are in, and we need only learn from them.

7. Relationships, Community, And Belonging — The Most Underrated Longevity "Drugs" We Have

Of all the discoveries in modern longevity science, perhaps none is more surprising – or more profoundly human – than this: The single strongest predictor of long-term health and lifespan is the quality of our relationships. This isn't the conclusion of a wellness guru or a self-help book. It's the core finding of the Harvard Study of Adult Development, the longest-running analysis of human health in history, spanning 85 years, three generations, and thousands of participants. After tracking biomarkers, genetics, income, habits, and life trajectories across decades, the Harvard researchers reached a startling conclusion: Warm, supportive relationships predict longer life, better health, and greater happiness more powerfully than cholesterol levels, socioeconomic status, IQ, or even genetics.

The data are anything but soft. In meta-analyses combining 300,000-plus subjects, strong social connection reduces the risk of premature death by up to 50% – a longevity effect comparable to quitting smoking and stronger than exercise or maintaining a healthy weight. Conversely, chronic loneliness and social isolation carry mortality risks on par with smoking 15 cigarettes a day. Loneliness and isolation can increase dementia risk by 50% and heighten the likelihood of cardiovascular disease, depression, and metabolic illness.

The mechanism is increasingly clear. High-quality relationships regulate the stress-response system, lower cortisol levels, and dampen chronic inflammation, the molecular accelerant of nearly every age-related disease. Social connection improves sleep quality, strengthens immune function, and preserves cognitive resilience. Community, in effect, is a powerful biological signal telling the body: *"you are safe."* And bodies that feel safe age more slowly.

If Japan teaches us to move more and eat less, the Harvard study teaches us something equally essential: we are built to belong. Evolution wired human health to thrive in the context of family, friendship, and community.

So how do we operationalize this insight in a Medicine 3.0 framework? I'm taking three specific steps:

1. ***I'm investing deliberately in my closest relationships:*** I schedule time with friends and family the way I schedule workouts or doctor visits. My aim is consistency: A standing weekly dinner, a recurring walk, a regular catch-up call that's not left to chance. I want to ensure that the relationships that matter most to me don't fade away. I aspire for the strength of these connections to compound over time – over decades – as the best "Forever Stocks" would.

2. ***I'm doubling down on my community:*** Most of us have an activity or practice we love that's shared with others, and often tied to our childhood. A sport. A religion or spiritual community. Hunting. Adventure travel. For me, it's the wonderful, weird world of Speech & Debate, in which I competed in high school, now coach my teenage daughter Daphne, and serve on the volunteer board of the National Speech & Debate Association. Which specific community doesn't matter – at least not for longevity and healthspan. What matters is the regularity of connection and bonding over a shared identity.

3. ***I'm aiming to build micro-connections into daily life:*** This one is tough for me, since by nature I'm an introvert. I'm content – sometimes most content – in solitude. But I've come to be a believer in proactively speaking with random people – the local barista, neighbor, travelers at the airport. The data show that these small interactions reduce stress markers and improve emotional tone for hours afterwards… even for introverts like me.

In adopting these practices, I'm looking to take advantage of the bottom-line result of the Harvard researchers: Good relationships don't just make life happier – they make life longer. For all the advances in genetic medicine, diagnostics, and longevity therapeutics, one truth remains stubbornly unchanged: The people we love and the communities we build may be the most powerful treatments for human health that exist.

Actions to Take: This month's recommendation is not a stock – it's a set of practices that will help you compound both your healthspan and lifespan… and live a longer, richer life. I've summarized these recommendations in the table below:

Medicine 3.0 Summary Table

Medicine 3.0 Category	Aims	Practices And Tools
Sleep	7 hours of sleep per night High sleep quality Sufficient deep sleep Sufficient REM sleep	Oura Ring Eight Sleep Pods
Cardiovascular Health	Baseline CVD risk assessment Ongoing CVD risk monitoring Aggressive intervention if early warning signs	CT angiogram or CAC score Regular biomarker checks • ApoB • Lp(a) • hs-CRP • Triglycerides • Fasting insulin For lipid management • PCSK9 inhibitors • Bempedoic acid • Avoid statins
Cancer Detection	Regular cancer surveillence Detect any cancers at Stage I or II	Prenuvo Whole Body MRI Eve Wellness Advanced Ultrasound
Brain Healthspan	Understand APOE risk Adopt simple prevention measures Follow emerging relevant siRNA therapies	APOE genetic testing Basic prevention strategies • Sleep quantity & quality • Regular exercise • Metabolic health maintenance • Oral and dental hygiene • Emotional well-being • Monitor developments in siRNA therapeutics
Metabolic Health	Avoid metabolic syndrome and insulin resistence	Apply five diagnostic criteria for metabolic syndrome Implement aggressive corrective steps if even two criteria are met
Lessons From Japan	Integrate higher activity levels into daily life Eat less	Measure daily step count Target 8,000 daily steps Understand your recommended daily caloric intake Target consuming 10% less than recommended
Relationships And Community	Invest in relationships and community Understand the profound impact they have on lifespan as well as healthspan Shift from "nice to have" to "must have"	Prioritize and schedule time for closest relationships Identify your community (sport, spiritual, travel, hobbies) and adopt active, regular participation Foster daily micro-connections, including with strangers

Portfolio Review

TECHFRONTIERS | PORTFOLIO

Ticker	Company	Entry D...	Entry Price	Price	Total Return	Status
Biotech						
SGMT	Sagimet Biosciences	01/09/2024	$5.71	$6.50	83.58%	Buy Up to $5.00*
ROIV	Roivant Sciences	02/29/2024	$11.44	$21.27	85.88%	Hold
TGTX	TG Therapeutics	07/03/2024	$18.79	$32.08	93.91%	Hold^^
SGMT	Sagimet Biosciences	09/05/2024	$2.62	$6.50	132.44%	Buy Up to $5.00***
BCYC	Bicycle Therapeutics	05/07/2025	$7.78	$7.15	-8.10%	Buy Up to $8.75
ACET	Adicet Bio	05/07/2025	$0.49	$0.56	14.19%	Buy Up to $0.75
ALNY	Alnylam Pharmaceuticals	06/04/2025	$305.31	$469.50	53.78%	Buy Up to $320
PRME	Prime Medicine	07/02/2025	$3.07	$4.02	68.19%	Buy Up to $4.00**
FBIO	Fortress Biotech	09/03/2025	$2.95	$2.80	-5.08%	Buy Up to $2.75
Blockchain Blue Chips						
8473:JP	SBI Holdings	02/05/2025	¥2,157.50	¥3,226.00	53.70%	Buy Up to ¥3,600^
SBET	SharpLink Gaming	10/08/2025	$17.57	$11.02	-37.27%	Buy Up to $19
China Tech Boom						
GDS	GDS Holdings	11/05/2025	$34.17	$34.32	0.44%	Buy Up to $36
Hedges & Other						
LBRT	Liberty Energy	12/04/2024	$18.32	$19.52	8.27%	Buy Up to $20.00

TECHFRONTIERS | CLOSED POSITIONS

Ticker	Company	Entry Date	Entry Price	Exit Date	Exit Price	Total Return
CYTT	Cytier Therapeutics	01/09/2024	$3.05	02/08/2024	$3.12	2.30%
VIR	Vir Biotechnology	01/09/2024	$10.18	03/18/2024	$10.68	4.91%
LYEL	Lyell Immunopharma	01/09/2024	$41.40	03/18/2024	$41.60	0.48%
STRO	Sutro Biopharma	01/09/2024	$40.30	03/18/2024	$39.10	-2.98%
NUVB	Nuvation Bio	01/09/2024	$1.51	03/18/2024	$2.26	49.67%

TECHFRONTIERS | CLOSED POSITIONS

Ticker	Company	Entry Date	Entry Price	Exit Date	Exit Price	Total Return
AVIR	Atea Pharmaceuticals	01/09/2024	$3.45	03/18/2024	$4.00	15.94%
KOD	Kodiak Sciences	01/09/2024	$3.16	03/18/2024	$5.94	87.82%
ATHA	Athira Pharma	01/09/2024	$28.65	03/18/2024	$24.90	-13.09%
CMRX	Chimerix	02/08/2024	$0.91	03/18/2024	$1.10	20.87%
VNDA	Vanda Pharmaceuticals	05/02/2024	$4.68	10/14/2024	$4.81	2.78%
DERM	Journey Medical	06/06/2024	$4.68	12/04/2024	$5.59	19.44%
NUVB	Nuvation Bio	11/06/2024	$2.54	12/04/2024	$2.75	8.27%
QURE	uniQure	01/09/2024	$6.62	12/10/2024	$15.30	131.12%
QURE	uniQure	10/02/2024	$4.54	12/10/2024	$15.30	237.00%
HUMA	Humacyte	01/09/2025	$4.68	03/26/2025	$2.00	-57.26%

A few of the names in our portfolio experienced some volatility in November.

Sagimet Biosciences (Nasdaq: SGMT), which remains **my single favorite *Tech Frontiers* holding**, has declined from $10 per share earlier this summer all the way down to around $6 per share today. Meanwhile, over the past half year, the news that Sagimet has delivered has been only positive – for instance, recent confirmation in a Phase III clinical trial in China that the company's flagship drug, Denifanstat, achieved "grand slam" results in acne. These results mean that Denifanstat is poised to be a blockbuster in two huge markets that exceed $10 billion in size each: fatty liver disease ("MASH") and acne. Despite the decline, *Tech Frontiers* subscribers who bought Sagimet when we last recommended it, in September 2024, are still sitting on handsome gains from our $2.62 entry price. If the price decline continues, I will strongly consider re-recommending Sagimet to subscribers who don't yet own shares – stay tuned. And for those subscribers who already own Sagimet, please don't worry: I'm confident that even if the stock continues to decline in the short term, we have very significant gains to come. Sagimet is, in my view, the most positively asymmetric stock in our portfolio and one of the most striking positive asymmetries I've encountered in my career.

SharpLink Gaming (SBET) shares have declined nearly 45% from our entry level two months ago in October, caught in the brutal sell-off that has overtaken the broader blockchain market, including Bitcoin. **I shared some mid-month reflections** with subscribers about this downturn a couple of weeks ago. Unfortunately, extreme volatility is an inherent characteristic of the emerging blockchain asset class. As I noted in our update, Bitcoin – the most Blue Chip blockchain asset – has seen three

separate instances over its young life during which it has sold off more than 85% from a recent high. In each case, it has re-bounded to make new highs within two years. I empathize with the discomfort subscribers feel watching a holding decline in price – this discomfort is completely human and relatable. But the investment thesis for Ethereum, and in turn for Ethereum treasury SharpLink, remains as strong as ever – even if, in retrospect, our recommendation was poorly timed. For subscribers who already own SharpLink, I recommend you hold your shares – I may yet recommend we double down if they decline further in price. For subscribers who don't yet own SharpLink, please hold off on buying shares for now. I'd like to respect the Wall Street adage "don't try to catch a falling knife." I will send an update when I think it's safe to step in and buy the shares again. And, to be clear, I'm confident that in the long-term, Ethereum – and SharpLink – will rebound to new highs.

GDS Holdings (Nasdaq: GDS), **last month's recommendation**, likewise got clipped in November's jitters about the sustainability of the artificial-intelligence ("AI") market, although shares have since recovered nicely. I would remind subscribers that although GDS is listed in the U.S., its underlying business is in China. And China's AI buildout is lagging that of the U.S. by a time cycle of about three years, which means it has a *lot* of catching up to do. GDS is extremely well-positioned to profit as a premier "picks-and-shovels" provider as China races to achieve its own AI infrastructure buildout.

SBI Holdings (TSE: 8473 JT) effected a two-for-one stock split on November 27, which it undertook to increase liquidity of the stock in Japan. In practice, this means that subscribers who owned shares in SBI received two shares for every one they owned before, while the stock's nominal price has halved. We will adjust our reference price and buy-up-to price accordingly. **Our investment thesis in SBI** remains intact and I continue to believe the shares' outlook over the coming two to three years is bright.

Prime Medicine (Nasdaq: PRME) shares are below our buy-up-to price of $4 for the first time in many months – indeed, the shares more than doubled **after we recommended them**. I think Prime shares are a steal at this price and would urge subscribers who don't yet own them to buy a full position.

Finally, a few year-end "housekeeping" items for the *Tech Frontiers* portfolio.

- I'm moving **Bicycle Therapeutics (Nasdaq: BCYC)** to a "hold" for the time being as I reassess the risk/reward in the stock. I'll update subscribers on Bicycle early in 2026.
- I'm lowering the buy-up-to price on Fortress Biotech (Nasdaq: FBIO) to $2.75 in the aftermath of the Complete Response Letter the company received from the FDA. I continue to **believe the long-term risk/reward in Fortress is excellent** – but I think it makes sense to reduce the ceiling at which we take advantage of the opportunity in light of the decline in the stock's price. For subscribers who already own Fortress, the stock is a "hold." I'm very confident about the company's long-term prospects.

- **Sell Alerts:** Finally, I am recommending subscribers exit shares of **Adicet Bio (Nasdaq: ACET)**, realizing a 10% gain from our recommendation of it in May, and **Liberty Energy (LBRT)**, for a 6% gain from a year ago – I foresee better opportunities for our capital than keeping them tied up in these companies.

Tech Frontiers "Best Buys"

For new subscribers, we highlight current portfolio picks that are at an attractive buy point. The current "Best Buys" are:

Shares of **Prime Medicine (Nasdaq: PRME)**, which we recommended in July, are just below our $4 buy-up-to price for the first time in many months. Prime shares are a steal at this price, and I would urge subscribers who don't yet own them to buy a full position while they can.

Shares of **Fortress Biotech (Nasdaq: FBIO)** declined following the Complete Response Letter the company received from the FDA. I continue to **believe the long-term risk/reward in Fortress is excellent** – but I think it makes sense to reduce the buy-up-to price to $2.75 in light of the decline in the stock's price. For subscribers who already own Fortress, the stock is a "hold." I'm very confident about the company's long-term prospects.

As 2025 approaches its end, I want to thank each and every one of you who reads *Tech Frontiers* for taking this journey with me. I love writing the newsletter month-to-month and am grateful for your trust and support. Wishing you and your families a terrific holiday season, and a healthy, flourishing 2026 in all the ways that truly matter –

Best regards,

Erez