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# MEDICINE 3.0

## INVESTING IN WAYS TO LIVE LONGER

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## Two Lists – For Your Health and For Your Investments

In 1936, in the thick of the Great Depression, an enterprising six year old began selling gum and Coca-Cola door to door in Omaha, Nebraska. At age eight, he progressed to delivering newspapers, eventually taking on three separate paper routes… then, still an adolescent, plowed his earnings into the purchase of pinball machines that he placed in local barbershops as well as a stake in a 40-acre farm, which generated passive income. He filed his first tax return when he was 14.

I'm guessing you've heard of this precocious Depression-era child… Warren E. Buffett.

In his youth, Buffett vowed that if he were not a millionaire by age 30, he would jump off the tallest building in Omaha. He missed that goal by a few years but then rocketed past it, as the $450,000 he invested in his own Buffett Partnerships appreciated to around $1.8 million by 1964 – a time when the median family income in the U.S. was $5,620 per year.

*Forbes* began publishing its list of the 400 richest Americans back in 1982, and not surprisingly, Buffett appeared on the very first list… and has re-appeared on every single one since then.

His hurry to amass wealth, and the single-minded focus with which he pursued this ambition from an age at which most kids are still learning to read, raise an interesting question:

How much of Buffett's wealth did he create after his 60th birthday?

The answer: 97.7%.

The math behind the answer is simple – Buffett's net worth at age 60 was $3.3 billion. His net worth today, at age 93, is $138.4 billion.

The *intuition* behind the answer is likely one that will be quite familiar to anyone who has ever built a discounted-cash-flow model: When compounding capital at a steady rate of return, the biggest gains in absolute dollars always come at the end.

To help make this intuition more concrete, consider: Buffett's long-term rate of return at Berkshire Hathaway has been 20%. If he were to grow his net worth by 20% in 2024, his 94th year of life, this would translate into a $27.6 billion gain… a one-year haul equal to his entire lifetime's net worth at age 67.

We can call the phenomenon I'm describing the "tail effect": In a long-run financial model, it's the tail end that generally drives the greatest dollar returns.

One curious implication of the tail effect is that if you care about maximizing your net worth, you should care deeply about longevity.

Of course, there are better reasons than wealth to care about longevity. The *World Happiness Report*, a collaboration led by renowned polling firm Gallup and Oxford University's Wellbeing Research Centre, studied the happiness of people at different stages of life. It found that Americans over age 60 are among the happiest people in the world, ranking in the top 10 among all age cohorts globally. What about America's young and middle aged? Both groups lie outside the top 50.

Though I'm still in my early 50s, I imagine many Porter & Co. subscribers intuitively get why we stand a better chance of coming closer to happiness as we get older. Capital is far from the only thing that compounds – so do learning, mastery, relationships, and the good decisions we make in our lives. These include picking the right life partner and investing our best selves in our kids and grandkids. Since these domains are subject to compounding, they too often demonstrate a tail effect – saving their sweetest, best rewards for last. But to enjoy these rewards, we've got to make it there… we've got to live long enough.

## The Many Benefits of Living Longer

This issue of *Biotech Frontiers* differs from those that have come before it and from most of the ones that will follow. We usually focus on a specific investment opportunity in biotech, which we explore through the seven-part framework we outlined in our ***Investment Guidebook***. We'll be doing that again next month and most other months in 2024.

But in this issue, we'll instead explore the theme of longevity. The lens we'll use is Dr. Peter Attia's magnificent book *Outlive: The Science & Art of Longevity*, which I originally mentioned in the *Guidebook*. Attia's book is one of the best I read last year, and I would strongly recommend it to anyone who cares about their own health and the health of their loved ones. But at 496 pages, it's a dense read.

So in this issue, I will distill for you the most important ideas I take away from *Outlive*, all of which are directly relevant to enhancing our longevity. However, I'm aiming for something more ambitious than good *CliffsNotes*. We'll also be building two useful lists:

First, a list of specific, actionable steps you can take to apply the most important ideas in *Outlive* to improve your own health.

Second, a watchlist of potential investment opportunities that flow from the key ideas about longevity that Attia lays out. Although I am not going to recommend any of these opportunities in this issue, I would be surprised if we don't return to them in the future. By exploring them here, interested subscribers can begin to track them on their own.

For those who like roadmaps, here's where we're headed:

We'll begin with two foundational concepts from *Outlive*: Healthspan and Medicine 3.0. These ideas are important because they frame every other idea in Attia's book… and every idea we'll explore in this issue.

From there, we'll introduce Dr. Attia's Four Horsemen – the four disease areas that are the likeliest causes of death for anyone 40 and older. We'll look at each of these four: where medicine has made advances against them, and where it has gotten stuck… what specific steps are available to take now to help forestall these diseases, and what kind of next-generation help may be available over the horizon… and finally, what companies are doing promising work against each disease.

We'll then briefly touch on the five tactical interventions Attia argues are relevant to fighting the Four Horsemen. These are: exercise, nutrition, sleep, emotional health, and exogenous supplements.

We'll close this issue with a brief Portfolio Review.

Let's get started…

## Lifespan, Healthspan, and Medicine 3.0

Most of us are already familiar with the idea of **lifespan** – simply, how long we live. Lifespan is binary: We're either alive or we're dead. One of the important arguments in *Outlive* is that today we stand a good chance of lengthening the lifespan we're "born" with due to our innate, individual biology… if we're willing to be proactive, and to embrace a new model of medicine.

But Dr. Attia also suggests that we need to widen our aperture and focus not only on lifespan, but also on **healthspan**. A narrow definition of healthspan is the period of life during which we're free from serious disease and disability. Yet there's a

richer and more useful definition too: Our healthspan is the period during which we're healthy enough to pursue the life we want, free from impairments that slow us down dramatically or cut us off from whole domains of activity.

Unlike lifespan, healthspan isn't binary. It's a continuum. Growing our healthspan requires taking steps that will enable us to still do the things we wish to do when we're older… from being fit enough to take a long hike with our grandkids to retaining the cognitive wherewithal to participate in a board game with our family, or to actively manage our investment portfolio.

Healthspan matters because for most Americans who grow old, the last decade of life is what Attia calls the **"Marginal Decade."** I'm guessing many subscribers have witnessed this process in parents, older siblings, and friends… or possibly even begun to experience it first-hand: Somewhere around age 75 (for most Americans), our physical and cognitive abilities begin to decline in an accelerated way. Our resilience – or our capacity to bounce back from setbacks to our health – atrophies significantly. We become more vulnerable to injury, illness, and disease. Sadly, for many, these last 10 years are a decade of diminishment and limitation.

One of *Outlive*'s most striking contentions is that by focusing on healthspan alongside lifespan, we can defer the onset of the Marginal Decade, or even eliminate it altogether. We can do this by attacking the root causes – a series of physiological insults and injuries that begin accumulating as early as our 30s, and accelerate into our 40s, 50s, and 60s – years and even decades *before* they become symptomatic in the form of actual disease. But to accomplish that ambitious aim, we need to shift our mindset as patients, and embrace a different mindset that Attia calls "**Medicine 3.0**."

Medicine 1.0 was practiced by the first very doctors starting over 2,000 years ago, exemplified by the Greek physician Hippocrates. The big idea it contributed was that diseases result from natural causes, not the actions of the gods. Relying principally on direct observation, the physicians of Medicine 1.0 nonetheless arrived at some helpful conclusions. Hippocrates, for instance, expounded his beliefs that walking for exercise promotes well-being, and that some foods have medicinal value while others are toxic.

Medicine 2.0 dates to the mid-19th century and the germ theory of disease – the idea that many diseases are caused by pathogens (e.g., bacteria, fungi, viruses, and other microorganisms collectively known as germs). Starting with the discovery of penicillin by Alexander Fleming in 1928, the physicians and scientists of Medicine 2.0 have given us an arsenal of drugs that have nearly doubled lifespans since the 1800s, largely by eliminating human mortality from infectious diseases such as polio, smallpox, and, more recently, HIV. Medicine 2.0 has had a transformational impact on humanity, but its focus has been largely on acute, infectious illnesses.

What Dr. Attia calls Medicine 3.0 encompasses several shifts. First, Medicine 3.0 emphasizes prevention more than treatment. It targets the root causes of disease *before* they become symptomatic in the form of illness, or, more important, before they reach the point of life-threatening emergency.

Second, Medicine 3.0 harnesses each individual's unique biological identity to generate strategies for prevention and treatment alike. An infectious disease such as polio is generally susceptible to the same antibiotics across all people. But cancer – like the other Four Horsemen – is a highly individualized disease, best prevented and treated by making use of what we know about an individual.

Third, Medicine 3.0 weighs the risks of doing something against the risks of doing nothing, or, put differently, recognizes that doing nothing can often be a high-risk choice. For example: The current standard of care in medicine might suggest no treatment for a patient who is pre-diabetic, because their blood glucose markers lie below the threshold for actual diabetes. Medicine 3.0 might look at the same patient and recommend aggressive changes to their diet as well as treatment with a drug such as metformin – weighing the risk that prediabetes will very likely blossom into diabetes, and simultaneously raise that patient's risk for a host of other serious illnesses associated with metabolic dysfunction (including cancer and dementia).

Fourth, as we've touched on, Medicine 3.0 focuses on healthspan as much lifespan. Indeed, the goal of Medicine 3.0 is not only to lengthen our lives… but, of equal importance, to increase our odds of prolonging a high *quality of life*. This emphasis creates a bias for action, as Medicine 3.0's approach is to do as much as possible today, well before diseases manifest, so that we can slow or delay the factors that underlie the Marginal Decade.

The final and most important shift that Medicine 3.0 militates is in the role of the patient. In Medicine 1.0 and 2.0, the patient is largely passive – he or she gratefully accepts the treatment that the physician offers. But in Medicine 3.0, the patient is the captain of their own ship. In Dr. Attia's words:

> *"Medicine 3.0 demands much more from you, the patient. You must be well-informed, medically literate to a reasonable degree, clear-eyed about your goals, and cognizant of the true nature of risk. You must be willing to change ingrained habits, accept new challenges, and venture outside of your comfort zone if necessary. You are always participating, never passive. You confront problems, even uncomfortable or scary ones, rather than ignoring them until it's too late. You have skin in the game, in a very literal sense. And you make important decisions."*

Next, we'll look at how Medicine 3.0 helps us better understand and combat the four big diseases that are the likeliest eventual causes of our mortality if we've reached age 40 – what Attia calls the Four Horsemen.

## The Four Horsemen

If we've reached age 40, the data tells us that we're likely to succumb eventually to one of four major life-threatening diseases:

- Heart disease
- Cancer
- Neurodegenerative disease (e.g., Alzheimer's)
- Type 2 diabetes and related metabolic dysfunction

In the argot of *Outlive*, each of these is a cause of "**slow death**" – slow in contrast to the causes of "**fast death**," such as an automobile accident or an acute infection. But also slow in the sense that each of these diseases begins to creep forward silently in the body years and even decades before a patient becomes symptomatic. Their slow, silent nature can be psychologically unsettling – for instance, for women who carry the BRCA1 gene associated with a greater risk of breast cancer, or for carriers of the APOE e4 gene associated with a significantly heightened risk of developing Alzheimer's. But for patients who embrace Medicine 3.0, the slow progression creates opportunity… the opportunity to intervene proactively before it has become too late.

Let's take a look at each of these Four Horsemen and what Medicine 3.0 can teach us about them.

### Horseman #1: Heart Disease

Heart disease runs in my family: My paternal grandmother suffered a heart attack in her 60s and had quadruple bypass surgery in its aftermath, while my biological father nearly died of a heart attack at age 62 and had multiple stents inserted as a result.

Heart disease is the first of the Four Horsemen because it's the leading cause of mortality in the United States, accounting for about 29% of all deaths annually. That's why one of the most important learnings I take away from *Outlive* is that heart disease is the most preventable of the Four Horsemen – and the only one that allows even people with a strong hereditary predisposition to the disease, like me, to dramatically change the odds in our favor with currently available interventions. As Dr. Attia writes, heart disease should be the 10th leading cause of death, not the first.

So why is it still the first? There are two big, interrelated problems with the way mainstream medicine today approaches heart disease. First, mainstream medicine

focuses on the wrong early warning signs. Second, as a result, mainstream medicine often intervenes too late – for example, after a patient has suffered a cardiac event, or after their risk for such an event has already increased significantly due to coronary artery disease. If we want to achieve dramatic risk reduction for heart disease – which we can do – we must address both problems.

Begin with mainstream medicine's focus on the wrong warning signs. I would wager that many subscribers have had their cholesterol levels tested and some of you have been warned that your "bad cholesterol" level – the LDL-C – is elevated. But as Attia argues convincingly in *Outlive*, LDL-C isn't a good predictor of heart disease. We need to focus instead on the two specific types of lipid particles that are the most telling warning signs of future atherosclerosis (the clogging of our arteries that directly causes heart attacks and strokes): apolipoprotein B ("apoB") and Lp(a) (pronounced "el-pee-little-A"). Both apoB and Lp(a) are measurable via readily available and affordable blood panels, but most mainstream physicians don't test for them. So the first step we need to take as Medicine 3.0 patients is to ask that we be tested for them in our next cholesterol screening, or to order the tests ourselves at a do-it-yourself venue such as Labcorp.

The second necessary shift in Medicine 3.0's approach to heart disease has to do with time. As Attia lays out, the physiological processes that culminate in deadly cardiac events play out very slowly – not over two or three or even five years, but over decades. Instead of asking, "What is my risk over the next five to 10 years?," we should be asking, "What is my risk over the rest of my life?"... a time span which, for many of us, probabilistically encompasses decades. Focusing on the latter question, Attia contends, will bring us to intervene at much earlier junctures to manage our apoB and Lp(a) levels aggressively.

The good news is that while mainstream medicine may not have the right approach to managing heart-disease risk, it does have many of the right tools – which we can deploy with a Medicine 3.0 mindset. A CT angiogram is an imaging test (shown

above) that can provide an informative baseline of whether our coronary arteries are damaged, as well as a quantitative measure of that damage via a calcium score. If a CT angiogram reveals that we are at risk, or if our blood panels for apoB and Lp(a) raise flags, mainstream medicine offers an armory of treatments to reduce the most dangerous lipids that clog our coronary arteries – including statins, PCSK9 inhibitors, and others. These treatments aren't perfect, but they can help achieve significant risk reduction for many patients *if* they're used early and aggressively enough. (For those readers who wish to delve more deeply into these treatments, Attia's discussion on pages 130-139 of *Outlive* is superb.)

What about next-generation medicines for heart disease… and which if any of these might be investable? It turns out that Lp(a), unlike apoB, has so far proven to be stubbornly resistant to significant downregulation by existing treatments such as statins. One hugely promising line of next-generation treatments for cardiac disease are novel drugs that may enable high-risk patients to bring down their Lp(a) levels without incurring dangerous side effects. Four companies are working on such drugs:

- Eli Lilly (NYSE: LILY) with its drug lepidosiren
- Novartis (NYSE: NVS) with pelacarsen, a drug it has licensed from Ionis
- Amgen (Nasdaq: AMGN) with olpasiran
- Silence Therapeutics (Nasdaq: SLN) with a compound called SLN360

The first three of these companies are Big Pharma giants. While a blockbuster success in the domain of heart disease would be an important triumph for any company – even for Big Pharma – the size of these first three companies means it's challenging for any early-stage drug to move the needle for them.

On the other hand, at only $1 billion in market capitalization, Silence Therapeutics is still a relatively small biotech company. A successful Lp(a) modulator would be a game-changing success for Silence, likely resulting in a multiplicative appreciation in its market value. And, it turns out, SLN360 is not the only intriguing project Silence has in its pipeline. For these reasons, we will be adding Silence Therapeutics to our *Biotech Frontiers* watchlist… stay tuned for more about it in the future.

### Horseman #2: Cancer

Cancer is the second leading cause of death in the United States, right behind heart disease. One in five Americans will have received some sort of cancer diagnosis by age 72. But whereas advances in medicine have enabled us to reduce mortality from heart disease by two-thirds since the middle of the 20th century, cancer still kills Americans at almost the same rate it did 75 years ago – despite tens of billions of dollars spent on the "war on cancer." As *Biotech Frontiers*

subscribers know from our coverage of **Dr. Steven Rosenberg** (pictured below) and Tumor Infiltrating Lymphocytes ("TIL"), science has made some remarkable advances in our understanding of this dread disease and in the tools we have to combat it. But we still have a long way to go.

Mainstream medicine today faces two interrelated obstacles in helping cancer patients. First, the armory of medicines we have to treat cancer is limited. For most local, solid-tumor cancers, the combination of surgery and radiation is fairly effective. But this approach, which is the best we've got, runs an unavoidable risk of leaving behind microscopic bits of cancer that may survive, proliferate, and then metastasize to other parts of the body. Furthermore, many patients receive their cancer diagnosis only after their cancer has already metastasized. And metastatic cancer is almost always a death sentence, albeit increasingly for some cancers, a slow one: chemotherapy and next-generation immunotherapies (such as CAR-Ts, TILs, and ADCs) can slow metastatic cancers, but they almost always come back, and are usually more resistant to treatment when they do.

The second problem with mainstream medicine's approach to cancer today is that we detect most cancer too late. As we've already discussed, small, localized cancers that haven't yet metastasized can be excised. For many such cancers, the long-term survival rates if the cancer is caught early enough (e.g., at stage I or stage II) are excellent. For example, the five-year survival rate for stage I breast cancer is 99%; for stage I colon cancer, 96.6%. Unfortunately, only about 42% of cancer cases are diagnosed at stage I or II – meaning 58% are caught at stage III and stage IV, when the cancer has either already spread to the lymph nodes or has metastasized to other organs. Put bluntly, the 58% of patients who receive their cancer diagnosis at stage III or IV are in the "too late" bucket. Some may survive and even be cured, but the odds patients in this category face are terrifying.

Physicians and scientists are hard at work on next-generation therapies that promise to expand our armory against cancer. We've already covered one of these

in *Biotech Frontiers* – **Iovance's TIL therapy**, which was the culmination of five decades of research by Dr. Rosenberg and his colleagues. I am also especially excited about the promise of another emerging area in cancer immunotherapy, antibody drug conjugates ("ADC").

If chemotherapy is akin to carpet bombing of the kind that the U.S. military practiced in Vietnam – indiscriminately destroying everything in its wake – ADCs are like precision-guided cruise missiles, able to find their way to a target (in this case, specific cancer cells) and deliver a toxic payload while leaving the surrounding areas largely unscathed. Several relatively small public biotech companies focus on ADC development, including ADC Therapeutics (NYSE: ADCT), Mersana Therapeutics (Nasdaq: MRSN), Sutro Biopharma (Nasdaq: STRO), and Vincerx (Nasdaq: VINC). I expect we'll dedicate an issue of *Biotech Frontiers* to this category of cancer therapeutics, probably later this year.

But as the TIL case study makes clear, getting next-generation therapies all the way from the lab through to regulatory approval and into the cancer clinic is an excruciatingly long, painstaking journey, which can take years and even decades. So meaningfully expanding our armory against cancer is something we can look forward to over the next one to two decades, but not something that's actionable for us as Medicine 3.0 practitioners today. Fortunately, we do have available – right now – two early-detection modalities for cancer that I believe are game changers. I would encourage every *Biotech Frontiers* subscriber to learn more about them and make use of them.

The first is whole-body magnetic resonance imaging ("MRI"). The leader in this domain is a private company called Prenuvo, which I first learned about from a podcast Dr. Attia did with its scientific founder back in 2019. At the time, Prenuvo only had a single clinic, in Vancouver. I flew there to learn more about the technology and have my first Prenuvo scan. Today, the company has nine clinics across major U.S. cities, with another 10 opening in the next year.

Prenuvo has designed a customized, cutting-edge MRI machine that enables it to complete a whole-body MRI in less than an hour – something that would take most standard hospital MRI machines over six hours. Prenuvo marries this advanced hardware with sophisticated, artificial-intelligence ("AI")-driven software that further enhances the resolution of its scans. The result: for about $2,500, and with no prescription or referral required, you can book a one-hour Prenuvo scan that detects over 95% of solid-tumor cancers at stage I or before. The scan is also able to detect a host of other serious health problems, including aneurysms, metabolic disorders such as fatty liver disease, spinal degeneration, and some auto-immune disorders (such as multiple sclerosis).

I've found the staff at Prenuvo to be exceptionally professional and kind, and the scan experience itself to be peaceful… Prenuvo even provides a comfortable headset that lets you watch Netflix while your scan takes place. Although it's expensive, my wife Danielle and I each get a Prenuvo scan once a year and consider it to be a cornerstone of our family's Medicine 3.0 approach to early cancer detection. (Full disclosure: I am a (very small) investor in Prenuvo's Series A financing, an investment I made after becoming a repeat Prenuvo patient for several years.)

The second important early-detection tool is liquid biopsy technology that relies on cell-free DNA. Here the leader is another private biotechnology company called Grail, which was spun out of Illumina (Nasdaq: ILMN). Grail's Galleri liquid biopsy test for cancer relies on the following deep scientific insight: As cancer cells grow, they shed cellular matter into the bloodstream, including bits of tumor DNA. These DNA sheddings are called cell-free DNA, because they are DNA that has been exfoliated from the cell itself. (DNA ordinarily resides inside a cell's nucleus.)

The Galleri test analyzes this cell-free DNA for a biochemical signature – known as a methylation pattern – that suggests the presence of cancer. Drawing upon high-throughput-screening technology, as well as AI, the Galleri test predicts whether cancer is present and, if so, which tissue type or organ it originated from. Galleri cannot detect every type of cancer, but the 50 types that it does encompass are a broad group. The test costs $949 and entails a simple blood draw – you do need a prescription to get one, but the Galleri website itself can connect you with telemedicine providers that can supply a prescription.

I consider Galleri a potent complement to Prenuvo. Together, for about $3,500 per year and an hour and a half of your time, these two exams can deploy two distinct, highly sophisticated methods – one based on high-resolution imaging, the other based on biochemical biomarkers in the blood – to detect cancer at the earliest stages, long before it's symptomatic. If you do end up finding cancer, identifying it at this early stage can dramatically improve your long-term prognosis.

One final note: While both Prenuvo and Grail are private companies, one or both may eventually go public. (Grail's original parent company Illumina sought to re-acquire Grail after spinning it out, but antitrust regulators have shot down the deal.) We will be watching both companies carefully to see if either IPOs, as I think the commercial prospects for both are exceptionally promising. I will update *Biotech Frontiers* subscribers if an opportunity emerges to invest in either of these.

### Horseman #3: Neurodegenerative Disease

The term "neurodegenerative disease" describes a family of illnesses that result from a breakdown of our neurons, the cells that make up our nervous system – including the brain, which is the center of our cognition, and our nerves, which facilitate movement. The best-known neurodegenerative disease is Alzheimer's, which afflicts nearly 7 million Americans. Other important neurodegenerative diseases include Lewy body dementia, which affects about 1.4 million Americans; and Parkinson's, which impacts about 1 million but is also the fastest growing of the group. Rarer conditions such as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) and Huntington's disease belong to this family as well.

Of the Four Horsemen, neurodegenerative disease and especially Alzheimer's have proven to be the most intractable. We have a far more limited understanding of the mechanistic causes of these illnesses than we do for heart disease, cancer, or type 2 diabetes and related metabolic disorders. And despite tens of billions of dollars that have been poured into developing medicines for this family of illnesses, our armamentarium to treat them is still incredibly limited. In the case of Alzheimer's specifically, none of the FDA-approved treatments are curative; and the two drugs that the agency has approved on the basis that they may help slow progression for those with mild disease have been beset with controversy about their efficacy.

Unfortunately, neither Dr. Attia nor I are very optimistic about medical research producing game-changing therapies for Alzheimer's in the coming decade. There is still too much we don't understand about what causes Azlheimer's.

To focus on just one important example: For decades, Alzheimer's research was dominated by a causal model known as the amyloid hypothesis – the idea that Alzheimer's is caused by a buildup of a specific type of protein plaques in the brain called amyloid beta. The amyloid hypothesis proceeded from an observation that virtually all Alzheimer's patients' brains feature a buildup of such plaques.

But as we learn in introductory courses on the scientific method, correlation is not causation. At least as of today, high-profile drugs that mitigate or reduce the buildup of amyloid beta in the brain – such as crenezumab – have not proven effective in helping Alzheimer's patients. At a minimum, the amyloid hypothesis seems to be an incomplete account of what's going on in Alzheimer's disease. In a worst-case scenario, it may ultimately prove to have been a red herring.

Because we still seem so far from agreement on Alzheimer's basic etiology, as a biotech investor I have shied away from investing in Alzheimer's-focused companies and will likely continue to do so. One of my oldest and closest friends is an MD/PhD who finished first in his class at Harvard Medical School and was promptly hired into the faculty there. This friend, who is widely regarded as one of the most brilliant scientists of his generation, has also launched several successful biotech companies. I hope to introduce him in more detail to *Biotech Frontiers* subscribers in a future issue, but for now, I'll refer to him simply as Dr. M.

Dr. M.'s advice to me has been more pointed: "Never invest in an Alzheimer's company. Alzheimer's is a graveyard for biotech investors." He first gave me this advice about two decades ago… he has not been wrong so far.

In part because prospects for an Alzheimer's miracle drug seem so distant, one of the most important learnings I take away from *Outlive* is that Alzheimer's **prevention** is well worth every Medicine 3.0 patient's investment of time. The entire idea of aiming to prevent Alzheimer's disease, or at least to significantly delay its onset, was novel to me until I read about it in *Outlive*. But Dr. Attia makes a compelling case that Alzheimer's prevention is a realistic goal grounded in good science. For subscribers who wish to zero-in on that case in more detail, it appears at pages 186-194 and 199-205. Here in brief are the five pillars of Attia's prevention strategy:

1. **Exercise:** Attia describes regular exercise as the single most powerful item in the preventative toolkit for Alzheimer's and other neurodegenerative diseases. Exercise promotes glucose homeostasis and the health of our vasculature – both of which, in turn, may mitigate the kind of chronic inflammation that increases neurodegenerative disease risk. He advocates for both endurance exercise and strength training specifically.

2. **Diet**: Attia suggests that following both Mediterranean-style and ketogenic diets may provide distinct benefits for Alzheimer's prevention. Both diets generally improve our glucose metabolism and help mitigate inflammation. Evidence from randomized, controlled trials indicates that ketogenic diets improve cognition and memory in subjects with early-stage Alzheimer's.

3. **Sleep**: Sleep deserves a much longer, more detailed treatment, which I may well make the focus of an entire future issue of *Biotech Frontiers*. For now, the key takeaway is that sleep, and especially deep sleep, is when our brain

heals itself. Sleep disruptions and poor sleep are major drivers of increased risk of dementia. So regularly getting enough sleep, and enough high-quality sleep, is a crucial part of Alzheimer's prevention. Danielle and I both wear Ōura rings to help us track our sleep quantity and quality – we have found that simply measuring these things helps us make better decisions to support them in our daily lives.

4. **Dental health**: A growing body of research links oral health, and especially the state of our gum tissue, to our overall health. Researchers have found that a microbe called *P. gingivalis* (the cause of gingivitis, or bad breath) is responsible for large increases in inflammatory markers such as IL-6. *P. gingivalis* has also shown up inside the brains of patients with Alzheimer's disease – though again, correlation is not causation. But the upshot is that regular brushing and flossing are potent, low-hanging fruit for Alzheimer's prevention.

5. **Dry saunas**: Another nugget that I was completely unaware of until reading *Outlive* is the potential health benefits of regular dry saunas. For those whose curiosity is piqued, Attia discusses these benefits on page 204. For those who want to go directly to the take away: At least four dry sauna sessions per week, of at least 20 minutes per session, at a temperature of 179 degrees Fahrenheit (82 degrees Celsius) or hotter, may help cut Alzheimer's risk by as much as 65%.

### Horseman #4: Type 2 Diabetes and Metabolic Dysfunction

Type 2 diabetes – formerly known as adult-onset diabetes – is characterized by insulin resistance (where insulin loses its efficacy in the body), a relative lack of insulin, and high blood sugar. Today, one in nine U.S. adults, or more than 11% of the U.S. population, is a type-2-diabetes sufferer. But I find two other statistics about the prevalence of this disease remarkable: More than 29% of U.S. adults over age 65 have type 2 diabetes, and another 38% of the overall U.S. adult population meets at least one criterion for pre-diabetes. All told, the data suggests that nearly half the U.S. population is either on the road to type 2 diabetes or already has it.

According to U.S. Centers for Disease Control, diabetes is only the eighth leading cause of death in the United States, causing about 100,000 deaths annually. Why then does Dr. Attia categorize it as the fourth Horseman? The answer constitutes another of the most important learnings I take away from *Outlive*: Because diabetes itself, and the metabolic dysfunction that generally precedes it, can dramatically elevate our risk for cardiovascular disease, cancer, and Alzheimer's. Indeed, Attia argues that we may eventually come to realize that diabetes and related metabolic dysfunction is the one thing that all of these other killers have in common. This last Horseman can directly cause our death by itself… but it can also summon each and all of the others.

Medicine 3.0's strategy for addressing type 2 diabetes has two prongs that should by now be familiar: First, zeroing in on a set of biomarkers that mainstream medicine largely ignores, with the aim of generating a much earlier warning signal that metabolic dysfunction may be taking root. Second, adopting aggressive, proactive behavioral changes that can prevent metabolic dysfunction and even reverse it if they're implemented consistently.

Mainstream medicine's gold standard for diagnosing a patient with type 2 diabetes is a HbA1c blood-test value above 6.5%. HbA1c measures the amount of glycosylated hemoglobin in the blood, which in turn allows us to estimate a patient's average level of blood glucose over the preceding 90 days. But as Dr. Attia argues convincingly, an HbA1c reading of, say, 6.2% or 6.3% – while below the accepted 6.5% threshold for type-2-diabetes diagnosis – may still indicate that things are on their way to being wrong.

To get a clearer picture and to get it earlier in a patient's progression toward metabolic illness, the Medicine 3.0 approach augments the HbA1c test with several others that mainstream medicine typically doesn't focus on. These include tests for elevated uric acid, elevated homocysteine, even mildly elevated ALT liver enzymes, and above all, insulin resistance – which Attia assays via an oral glucose-tolerance test.

The good news about the fourth Horseman is that it's the most treatable of the group. While type 2 diabetes itself doesn't have a cure, the right, aggressive changes to diet, exercise, and sleep can reverse its symptoms, and hold blood sugar levels at safe levels without medications or even insulin. Attia's chapter on type 2 diabetes and metabolic dysfunction ends with a wonderfully pithy line: One can think of this complex of disorders as the result of the "overfeeding, undermoving, and undersleeping" that are chronic to much of modern life. Here, Medicine 3.0's directive is a return to our ancestral selves: When humans ate in moderation, moved our bodies regularly, and didn't associate lack of sleep with a busy, important life that confers high status.

## Five Tactical Domains Across the Four Horsemen

In the second half of *Outlive*, Dr. Attia explores in detail five tactical domains that can have a powerful, positive impact across the Four Horsemen. These are:

1. **Exercise** – including aerobic efficiency, aerobic output, strength and stability
2. **Nutritional biochemistry** – what, when, and how much we eat
3. **Sleep** – why it matters and why modern medicine has only recently begun to realize its relevance to healthspan
4. **Emotional health** – which, like type 2 diabetes, can dramatically increase

or reduce the risks posed by all of the Horsemen, as well as constituting an important driver of healthspan in its own right

5. **Exogenous molecules** – the various drugs, supplements, and hormones that can help move the needle in a positive direction for healthspan, if curated and consumed with care

While I can't double click on each of these in this issue, I look forward to exploring some of them in *Biotech Frontiers*. Several of these themes – for instance, exercise, sleep, and emotional health – are hugely fertile scientifically and also ripe for investment. One of the negative-enterprise-value ("EV") biotech companies that narrowly missed our initial basket of 10 stocks, but which we may well revisit, is Vanda Pharmaceuticals (Nasdaq: VNDA). A cornerstone of Vanda's portfolio is its drug Hetlioz, which treats sleep disorders. Another name on my watchlist, NRx Pharmaceuticals (Nasdaq: NRXP), is developing the first FDA-sanctioned ketamine therapy for acute suicidality – a mental-health epidemic in the United States with almost no effective and FDA-approved treatments. So stay tuned: We will return to the themes that Attia explores in the second half of *Outlive* again.

## Summing It Up: Two Lists

Earlier in this issue, I promised you we'd come away with two lists: First, a list of the specific, actionable steps you can apply from *Outlive* to improve your own vigilance against the Four Horsemen to extend your healthspan. Second, a watchlist of potential investments for us to keep a careful eye on as we journey. Here are both lists:

| Actionable Items for Healthspan | Investment Watchlist |
|---|---|
| **Heart Disease** | |
| apo(b) test<br>Lp(a) test<br>CT angiogram<br>Calcium score | Silence Therapeutics (Nasdaq: SLN) |
| **Cancer** | |
| Prenuvo Whole Body MRI<br>Grail Galleri liquid biopsy | ADC companies<br>ADC Therapeutics (NYSE: ADCT)<br>Mersana Therapeutics (Nasdaq: MRSN)<br>Sutro Biopharma (Nasdaq: STRO)<br>Vincerx Pharma (Nasdaq: VINC)<br><br>Early Detection & Monitoring<br>Prenuvo (private)<br>Grail (private) |
| **Neurodegenerative Disease** | |
| Preventative modalities<br>Exercise for endurance and strength<br>Mediterranean and Ketogenic diets<br>Sleep quantity and quality<br>Dental health<br>Dry sauna (>179 degrees, 4x/week) | Higher bar for potential investments |
| **Type 2 Diabetes and Metabolic Disorders** | |
| Oral glucose tolerance to test insulin resistance<br>Uric acid<br>Homocysteine<br>ALT liver enzymes | |
| **5 Tactical Approaches for the Four Horsemen** | |
| Exercise<br>Nutritional biochemistry<br>Sleep<br>Emotional health<br>Exogenous molecules | Vanda Pharmaceuticals (Nasdaq: VNDA)<br>NRx Pharmaceuticals (Nasdaq: NRXP) |

Since my childhood, I've been a voracious reader... and I still aspire to read between 25 and 50 books per year. *Outlive* feels like one of the most consequential books I've ever read. Sharing these reflections with you has been a labor of love. If you take the ideas in *Outlive* seriously, they stand a chance to add years to your life – which can change your net worth for the better, as well as so many other things that are even more important.

# Portfolio Review

## BIOTECH FRONTIERS PORTFOLIO

| Ticker / Link to Latest Update | Entry Date | Entry Price | Latest Close | Total Return | Status |
|---|---|---|---|---|---|
| **Open Positions** | | | | | |
| QURE Uniqure | 01/09/2024 | $6.62 | $5.20 | -21.45% | Hold |
| SGMT SAGIMET BIOSCN-A | 01/09/2024 | $5.71 | $5.45 | 71.26% | Buy Under $6.75* |
| IOVA IOVANCE BTHRPTCS | 02/05/2024 | $7.92 | $13.60 | 71.72% | Hold |
| ROIV ROIVANT SCIENCES | 02/29/2024 | $11.44 | $11.51 | 0.61% | Buy Under $13.00 |

## BIOTECH FRONTIERS CLOSED POSITIONS

| Ticker | Entry Date | Entry Price | Exit Date | Exit Price | Total Return |
|---|---|---|---|---|---|
| VIR VIR BIOTECHNOLOG | 01/09/2024 | $10.18 | 03/18/2024 | $10.68 | 4.91% |
| LYEL LYELL IMMUNPHRM | 01/09/2024 | $2.07 | 03/18/2024 | $2.08 | 0.48% |
| STRO SUTRO BIOPHARMA | 01/09/2024 | $4.03 | 03/18/2024 | $3.91 | -2.98% |
| NUVB NUVATION BIO-A | 01/09/2024 | $1.51 | 03/18/2024 | $2.26 | 49.67% |
| AVIR ATEA PHARMA | 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 | $2.87 | 03/18/2024 | $2.49 | -13.09% |
| CYTT Cyteir Therap | 01/09/2024 | $3.05 | 02/08/2024 | $3.12 | 2.30% |
| CMRX Chimerix | 02/08/2024 | $0.91 | 03/18/2024 | $1.10 | 20.87% |

## BIOTECH FRONTIERS WATCHLIST

| Ticker | Initial Analysis | Latest Close |
|---|---|---|
| ADCT ADC Therapeutic N | 04/04/2024 | $4.71 |
| ATHA ATHIRA PHARMA | 01/09/2024 | $2.50 |
| AVIR ATEA PHARMA | 01/09/2024 | $3.85 |
| CMRX Chimerix | 02/08/2024 | $1.04 |
| KOD KODIAK SCIENCES | 01/09/2024 | $4.08 |
| LYEL LYELL IMMUNPHRM | 01/09/2024 | $2.09 |
| MRSN MERSANA THERAP | 04/04/2024 | $4.25 |
| NRXP NRX Pharma | 04/04/2024 | $5.20 |
| NUVB NUVATION BIO-A | 01/09/2024 | $3.48 |
| SLN SILENCE THER SP ADR | 04/04/2024 | $21.42 |
| STRO SUTRO BIOPHARMA | 01/09/2024 | $4.92 |
| VINC Vincerx Pharma | 04/04/2024 | $5.92 |
| VIR VIR BIOTECHNOLOG | 01/09/2024 | $9.47 |
| VNDA Vanda Pharma | 04/04/2024 | $4.92 |

****Total Return** reflects selling 1/2 of Sagimet Bio (SGMT) on January 22, 2024 for $18.42 per share and re-suming a full position on February 8, 2024, up to $6.75 per share.*

*****Total Return** reflects selling 1/2 of Kodiak Sciences (KOD) on March 5, 2024 for $6.20 per share.*

Note: This is a model portfolio based on hypothetical holdings. Please consult with a financial advisor before investing. You buy, hold, and sell at your own discretion and your own risk.

On March 19, I issued an update recommending a series of sales to our Biotech Frontiers portfolio, driven by a disconnect between the market's expectation of Federal Reserve rate cuts and the probability I ascribe to the Fed's actually being able to deliver those cuts in light of inflation. I reiterated how incredibly sensitive biotech stocks are to interest rates… ground which we covered in detail in our ***Investment Guidebook***.

In the short time that has passed since I sent that update, the market has moved closer to the point of view I laid out, with major stock indexes as well as biotech selling off. To take one example, we sold half of our position in **Kodiak Sciences (Nasdaq: KOD)** – one of the original 10 stocks in our basket of negative-EV biotechs – when it hit $6.30, up 100% from our initiation price. We sold the other half on March 20 at $5.78. Kodiak has since declined to $4.08, down 29% from our second sale, in keeping with a decline in the overall biotech sector.

Kodiak is only one stock, and it's too early to tell if my exit call will be proven out. But I see my role as giving you the same advice I'd give my parents or siblings… and the thinking I follow with actions in my own portfolio. From that standpoint, I feel even better about the exit call than I did a few weeks ago.

When I ran money for Julian Robertson and others at Sabertooth Capital Management with my old partner Craig, we had an axiom: "Position yourself to play offense." By locking in some profits we've made since *Biotech Frontiers* launched, and shrinking the size of our portfolio as well as our dollar exposure, we've positioned ourselves to play offense. This biotech bear market still offers us a historic opportunity, and we're now even better situated to take advantage of it when the time is right.

The remaining companies in our portfolio are **Iovance Biotherapeutics (Nasdaq: IOVA)**, **Roivant Sciences (Nasdaq: ROIV)**, **Sagimet Biosciences (Nasdaq: SGMT)**, and **uniQure (Nasdaq: QURE)**.

Only Roivant has material update.

Earlier this week, in federal district court, Roivant and its joint-venture partner Arbutus Pharma won an important ruling against Moderna in their patent litigation. The ruling delivered the outcome of the Markman hearing, where the judge interprets the words and phrases in the patent at issue through a process lawyers call "claim construction." These rulings are important, because the way a patent gets interpreted (or "construed") by the court often determines which party will ultimately prevail on a claim of patent infringement. In this instance, Roivant and Arbutus prevailed in three of the four patents at issue in the hearing. I touched base with Mr. X – the world-class patent lawyer we're working with on this part of our Roivant investment thesis – and he agrees that the ruling increases the likelihood Arbutus and Roivant prevail against Moderna.

Roivant also announced two other pieces of good news in early April: a $1.5 billion stock-buyback program as well as exceptionally positive top-line results in its Phase II NEPTUNE clinical study for brepocitinib. Subscribers may recall we touched on brepocitinib as one of the potential blockbusters in Roivant's development pipeline... and although I haven't yet had a chance to review in detail the top-line Phase II results, based on a first pass, they look like a grand-slam success to me.

There's no change to my buy recommendation... I will only add that the risk/reward in Roivant stock has gotten even better than when we first recommended it.

If you haven't yet had a chance to see them, I'd encourage you to listen to my conversation with **Porter on asset allocation**, and with publisher Kim Iskyan in our first **Biotech Frontiers Open Forum**. Please share your feedback on either or both – my goal is to create content that's useful for you.

Best regards,

Erez