CURALINK

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thecurafoundation.org

Welcome to CuraLink—a newsletter for innovators building a healthier future for all.

Dear Cura Community,

Welcome back to CuraLink, a newsletter and interview series featuring the most pressing issues in human health, unmet medical needs and the emerging innovations and technologies directed to address them.

In issue 17 of CuraLink, we shared an inspiring conversation with Dr. Kizzmekia Corbett, one of the scientists responsible for the development of the lifesaving COVID-19 vaccines. Dr. Corbett discussed how to leverage science for the public good and the best strategies to prevent another pandemic. Read this interview at bit.ly/CuraLink-17.

In the quest to live longer, healthier, people often go to extremes. Every year, wellness companies sell restrictive diets, detox programs and experimental treatments with the promise to preserve youth. But in a largely unregulated market, few are backed by solid evidence.

In this month's CuraLink, we asked longevity expert, Dr. Nir Barzilai, to share his top anti-aging advice, the latest breakthroughs in the field and why aging is the mother of all diseases.

Robin L. Smith, MD
Founder, President and Chairman, Cura Foundation

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A conversation with Dr. Nir Barzilai

For over 30 years, Dr. Nir Barzilai has worked to unravel the biology of aging. Dr. Barzilai studies key mechanisms involving it, including how genetics, nutrients and environmental factors influence lifespan. He also investigates the physical and mental declines associated with aging and how they affect longevity. Treatments for age-related diseases like type 2 diabetes are being developed based on Dr. Barzilai's work and some are now in clinical trials.

Currently, Dr. Barzilai is focused on three projects: the Longevity Genes Project at the Albert Einstein College of Medicine, which is a study of centenarians and their families, the Targeting Aging with MEtformin (TAME) trial designed to prove the concept that multi-morbidities of aging can be delayed by metformin and a comprehensive study to identify proteins as biomarkers of aging that can be manipulated by drugs or genetics.

Contrary to popular belief that late life always involves pain and suffering, Dr. Barzilai's research shows that the aging process can actually be slowed—and even reversed. In the following interview, Dr. Barzilai shares insights from his research on SuperAgers and how drugs like metformin, SGLT2 inhibitors and GLP-1 agonists may modulate aging.

Nir Barzilai, MD, The Rennert Chair of Aging Research, Professor of Medicine and Genetics, Director of Institute for Aging Research, Director of Paul F. Glenn Center for the Biology of Human Aging Research and Director of NIH's Nathan Shock Center of Excellence in the Basic Biology of Aging, Albert Einstein College of Medicine

What sparked your interest in studying aging and longevity?

I became interested in aging when I was 13. My grandfather and I used to walk every Saturday. He had white hair, was obese and walked slowly. During our walks, he would tell me what he did when he was young. And I thought: Something is wrong here. There is no way he did what he described. How did he get to where he is now?

As I went on to become a medic in the army, a medical student, a physician, internist and endocrinologist, my main question was always: What is the biology of aging?

This question fascinated me. But it is still surprising to me that I became a pioneer in gerontology. There are many people interested in the topic, but not many who are investigating it in a scientific way.

Some of that stems from the fact that our parents often tell us that there is nothing we can do about death or aging. Yes, there's nothing to do about death in the future as we see it now. But aging? Absolutely. Going from hope to promise was a major turning point in my life.

Was there a moment where you realized that we could slow aging and that it doesn't have to be full of pain and suffering?

Whenever we started to discuss a patient in residency, one of my attendings would ask: "Does this patient look younger or older than their actual age?" When you start thinking that way, you see that there is a biological and chronological age. They're not the same. This approach impacts how you treat a patient. There could be a 68-year-old woman with pneumonia who is biologically old and dilapidated, so the prognosis is not good. Another 68-year-old woman looks like she is 50 and will recover from pneumonia, no problem.

So looking at biological versus chronological age gives you this perspective that aging can be modulated via genetics and the environment.

One example is caloric restriction: For years, we have been using caloric restriction as a control condition in scientific research. You take a group of animals—rodents, dogs, spiders or fish. Some eat whatever they want, while others' caloric intake is restricted by 30 or 40%. The restricted group is much healthier and lives about 40% longer. Caloric restriction is a simple intervention that connects aging and lifespan to the fact that it's modifiable.

Research has gone even further. In the genes of simple animals, we can impair one gene, and they live three times longer.

"Aging is modifiable."

People argue that animal research doesn't apply to humans. But all animals age in similar ways. There are several drugs that you can give to all animals, and it will affect the rate of their aging.

How do you define aging? What should people understand about the so-called hallmarks of aging?

Aging is a functional decline. People become unable to do things they normally could. Aging happens throughout life, but it accelerates after the age of 60. After 60, we start to accumulate disease after disease and need treatment after treatment, and our quality of life decreases.

Aging is not only about old age. People who survive cancer, live with HIV or undergo chemotherapy and radiation age more rapidly.

How has the field of gerontology evolved?

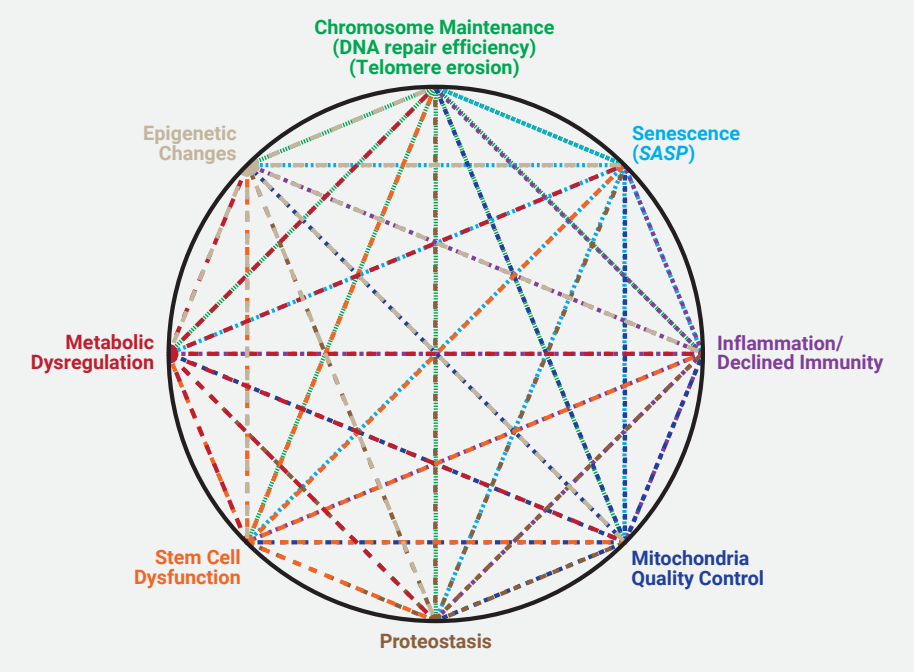
For over 100,000 years of human evolution, life expectancy was about 20 to 30 years. In the last 150 years, average life expectancy jumped three times higher, which is remarkable. It increased because we harnessed agriculture, cleaned our water sources, built sewers and vaccinated communities. We invested in public health and prevention.

With that extension, we started to see diseases that were not historically part of human life. People didn't die from Alzheimer's, cancer, diabetes and cardiovascular disease when they were 20 or 30 years old. So to address these new diseases, the National Institutes of Health (NIH) created institutes for various diseases such as the National Cancer Institute and the National Heart, Lung, and Blood Institute. But these institutes have become siloed. In my opinion, they are not institutes of health; they are institutes of diseases: The only true institute of health is the National Institute on Aging, which is focused on preventing a variety of diseases by targeting the biology of aging. These silos are terrible. Historically, funding organizations would say they are focused on singular diseases, not aging, and would not fund aging research. But the most influential risk factor for cardiovascular disease is aging; it's 1,000 times more predictive than cholesterol.

The field of gerontology has matured so much that people are noticing. One important fact is that the bulk of research on diseases like cancer, Alzheimer's and diabetes was done on young animals. But their biology is totally different compared to old animals. Researchers were using the wrong template. It's no wonder that the drugs they were developing were not effective. We were so successful in our research that those institutes now give extra grants to study the same things in old animals. Even when the science clearly shows a gap like this, it's difficult to change. Everyone wants to continue the way they initially organized.

What should everyone understand about the biology of aging, the hallmarks of aging and its underlying mechanisms?

What defines a hallmark of aging? Something has to go wrong as you age. If you can fix it in the lab via interventions like genetic manipulation or medication, then your animal is going to live healthier and longer. That constitutes a hallmark of aging.



Aging is a functional decline that happens throughout life and accelerates after age 60. The hallmarks of aging are biochemical changes that lead to impaired function, progressive loss of physiological integrity and increased vulnerability to death. These include: chromosome maintenance, senescence, inflammation and declined immunity, mitochondria quality control, proteostasis, stem cell dysfunction, metabolic dysregulation and epigenetic changes

There are up to 12 hallmarks of aging. All of these hallmarks are interconnected. In other words, you don't have to fix all of them together to be healthier; if you fix one, it improves the others. This is a great opportunity, therapeutically. That is why there has been over $40 billion of investment in longevity biotech companies even during this economic downturn. These companies are choosing one hallmark as a target, and if they can improve it, they can affect other hallmarks and have more indications of how to develop effective drugs.

Should we reclassify aging as a medical condition or disease?

"Aging is the mother of all diseases."

You can be born with the genes for Alzheimer's, but you're not born demented, and you're not demented at 1, 10 or 50 years old; it takes 60 or 70 years to manifest. Aging drives disease, and we want to prevent disease by preventing aging.

However, there is a huge sensitivity around ageism. First of all, the elderly that we want to help don't want to be called diseased or sick. The U.S. Food and Drug Administration (FDA), the American Federation for Aging Research and AARP don't want to call aging a disease. Not only that, what happened during COVID-19? We isolated the elderly, put them in institutions and prohibited their families from visiting—actions that exemplify how we treat them.

Through our Targeting Aging with MEtformin (TAME) trial, we are using metformin as a tool to show that if we prevent aging, we prevent many diseases and mortality. Once we show success in that trial, I think it will be easier for people to accept the idea of aging as a disease. Not everybody agrees with me. Ultimately, to make progress we don't need to call it that.

How can metformin delay aging and age-related diseases? Should everyone be taking metformin as they age?

Metformin is an extract of French lilacs. It's modulated, so it's a drug, but it's also a type of nutraceutical. People have known since the 1920s that it can be helpful for a variety of health issues: to prevent arthritis, flu and malaria, for example. But then people discovered that it lowers glucose in diabetics. Interestingly, it doesn't lower glucose in non-diabetics. It affects insulin levels.

Over the last 70 or 80 years, billions of people have taken metformin. Over time, we have discovered lots of interesting things. We've seen that if you don't have diabetes and you take metformin, it can prevent diabetes. If you have diabetes, it can help prevent cardiovascular disease. There are over 250 studies that show that people taking metformin have less cancer of all different types. There are association and clinical studies that show that it can prevent cognitive decline, dementia and macular degeneration. There's a lot of research showing that it prevents mortality, and when you give it to a variety of animals, they live longer.

One of the most interesting examples relates to immunity. Studies show that giving metformin within the first three days of a COVID-19 infection prevented hospitalization and death by 50% and Long COVID by 50%. So metformin not only targets one of the hallmarks of aging, which is immune decline, but it also prepares the body to deal with more severe disease. This is an example of how this drug may be really important for every challenge that we face when we get older.

But it's not for everyone. One of my challenges is to tell young people not to take metformin. Things that can be good when you're old can be harmful when you're young because of changing biology. Autoimmune diseases might be exacerbated if you take metformin when you're young.

What progress has your team made in understanding longevity and developing effective anti-aging interventions?

My team runs centenarian studies that include 750 centenarians and their families—more than 3,000 people in total. We have found that centenarians not only live longer; they live 20 to 30 years healthier than other people. So their lifespan and healthspan go together.

Centenarians also experience a contraction of morbidity. They're sick for very little time at the end of their lives. The Centers for Disease Control and Prevention data shows that the medical expense in the last two years of those who die after 100 is a third of those who die when they're 70. So there's a massive longevity dividend.

In fact, Andrew J. Scott, D.Phil, a professor of economics, argues that there is an additional economic advantage. What are centenarians doing if they aren't in the hospital? They are traveling, shopping and spending money. The potential economic value of this longevity dividend could be about $367 trillion over 10 years.

"Centenarians show that humans have the capacity to live long."

We have this in our genes, so how can we make drugs that mimic that genetic effect? Of these centenarians, 60% have a genetic variant that affects their growth hormones. When you are young high levels of growth hormones are better for reproduction, cognition and disease prevention. But this totally switches after the age of 50. Because when your body starts breaking down, you have to switch your energy from using it for growth to deal with repair. So if you have a mutation that impairs growth hormones, you're much more likely to live longer and healthier.

How are these insights from centenarians useful for everyone else?

Centenarians sometimes ask me: "Hey, what do you have for me?" But I don't have anything for them. I'm trying to imitate them. In a project I am leading called SuperAgers, we are recruiting 10,000 families of centenarians to identify as many longevity genes as possible. We have analyzed the SuperAgers' genetics and developed drugs based on our findings.

We are currently missing biomarkers for determining people's biological age. The FDA is very interested in a test that could be given at midlife, around 50. If someone is biologically 40, they may need a colonoscopy. But if they are biologically 60, they need to be taken care of more intensively.

Because aging is so complex, developing a test like this isn't easy. I'm currently looking at proteins as biomarkers. In our lab, we measured 5,000 proteins in each individual of our study population. We looked at which proteins are elevated between ages 65 and 95. What does it mean? Which ones should increase or decrease? We can also determine from those proteins where they're coming from. So if you have more proteins coming from the brain, we should be more worried about brain health. If it's from the liver, let's focus there. Aging doesn't progress symmetrically; we're going to fail in one organ before another.

Kahn siblings recreating a family photo in 1999. The siblings, Helen, Peter, Lee, (left to right) and Irving (front) were the oldest living quartet. Helen and Irving lived past 109, while Lee and Peter lived to 101 and 103

Where are we on the path to developing effective anti-aging medications?

My answer to that question has changed recently, certainly when it comes to metformin. With metformin, I used to say: Until I'm finished with the TAME trial, people shouldn't do anything with this drug. But the truth is that there is overwhelming evidence showing that metformin targets aging. There's another set of drugs called SGLT2 inhibitors, which were also developed to prevent diabetes and are kind of anti-aging drugs. They can also help prevent heart disease, kidney failure and cognitive decline.

Any doctor can repurpose a drug. I'm the founder of the Healthy Longevity Medicine Society. We are beginning to train longevity doctors and will eventually make recommendations for clinical practice. I think we should harness FDA-approved drugs for longevity—those that are already used widely, evidence-based and safe. There are 12 such drugs. Maybe we don't have all the information we want on all of them, but we do have good data on four or five. Perhaps those drugs could be prescribed already.

A relevant example is how metformin is useful for polycystic ovarian syndrome (PCOS). We better understand how it works now, but nobody studied that when we started prescribing it for PCOS. Clinicians just started experimenting. I think when drugs are so safe, and their major side effect is longevity, then why not?

GLP-1 agonist medications are increasingly used for obesity, diabetes and metabolic disorders. What should people understand about the benefits and risks of those drugs and could they be used to influence aging?

Dr. Barzilai at the Milken Institute Future of Health Summit in December 2022

Let's first circle back to caloric restriction and longevity. When we study that link in animals, we are also looking for caloric mimetics—drugs that will give the effect of reducing calories. GLP-1 agonists like Ozempic are perfect drugs. It took me a while to come off the fence. But it's not only about obesity. When you give this drug to younger animals that are not obese, they also live longer without losing weight. Obesity accelerates aging. So if you can fight that, you're really doing well from an aging perspective, too.

In my mind, these are gerotherapeutics. GLP-1 agonist medications are going to be an important tool in the fight against aging. With GLP-1 agonists, diabetics better manage their glucose, lose weight and improve their health. Currently, there are a lot of problems with getting these drugs to them, because people are using them for obesity, which is fine, but it's not the top priority. We need to get them to the diabetic people who really need them.

The second problem is that these drugs are used chronically. Every drug has trade-offs, but we don't yet know the trade-offs here. What happens when you lose enough weight and stop the drug? Will you become obese again? I heard that the FDA was concerned about malnutrition if the drug is overused. Anorexic people are using this drug to lose weight—that's not healthy. So there are trade-offs that still need to be discovered. We need to use personalized medicine to guide this kind of treatment.

Beyond medication, what do you do to live healthier, longer?

People can do a lot by improving their nutrition, exercise, sleeping and social connectivity. Developing healthy habits in these arenas is going to keep you healthy beyond the age of 80 for sure.

Let's focus on nutrition. Nutrition is a newly invented field that has made some terrible assumptions about what's good for us, including that breakfast is important. It may be important for kids, but, across human history, adults haven't typically eaten breakfast. Similarly, the idea that 65% of your diet should be carbohydrates drove a lot of obesity.

There's an interesting experiment in animals that has broader nutritional implications. In one condition, we gave a days' calories to animals in the morning. They were hungry and ate all the food within an hour. Then they fasted for almost 23 hours. When we took those same animals and fed them throughout the day, they were leaner, but they didn't live much longer. In other words, fasting is part of the longevity of those animals. That's where intermittent fasting is beneficial.

Fasting is an important tool for aging, not weight loss. I fast at least 16 hours every day. It's relatively easy to do. Men lose weight by fasting more than women. There can be an increase in exercise performance as well. Based on our research on aging, fasting is much more important than the foods you eat. Not that nutrition isn't important, but fasting is much more important. Then, if you eat a Mediterranean diet or lower your carbohydrate intake, that's even better.

What is the most important question in the field of aging that's yet to be answered?

This is my guiding question: How can we reprogram ourselves to believe we are young? This happens naturally in conception: You can take the sperm of a 90-year-old man and an egg of a 50-year-old woman, but in the process of reproduction, this age is erased. Our cells don't start at the age of our parents. So how can we achieve this for all of us?

In 50 years, I want to have the "Peter Pan" option. I want to give younger people an injection every few months or every year and actually erase aging. How can we do that? It's about staying young and healthy for longer. It's much harder to take somebody my age and make them younger. We can improve their health, but it's much easier to preserve youth and health.

This interview has been edited for length and clarity.

Insights, Perspectives & Ideas

Why Cancer Treatments Might Not Work Very Well for Older Adults

Undark, June 2023

Older people are more likely to be diagnosed with cancer than younger ones. Clinical drug trials, however, exclude older participants for a variety of reasons. Yet, cancer treatments effective in younger people can be toxic in older individuals. Jyoti Madhusoodanan explains that physicians treating geriatric cancer patients often tweak the dose or duration to limit side effects. Dr. Supriya Mohile, a geriatric oncologist at the University of Rochester thinks that the geriatric assessment, a tool to determine a person's biological age, "needs to be implemented until we have better clinical trial data." This may help mitigate under-treatment of those who might benefit from chemotherapy and over-treatment of those at risk of serious side effects.

PEPFAR at 20—A Game-Changing Impact on HIV in Africa

The New England Journal of Medicine, July 2023

In 2003, antiretroviral therapy (ART) transformed AIDS into a chronic condition in industrialized countries. However, in sub-Saharan Africa, fewer than 50,000 of the 27 million people living with HIV had access to it. President George W. Bush launched the President's Emergency Plan for AIDS Relief (PEPFAR) in 2003 in 15 countries with high HIV burdens. As of 2022, PEPFAR-supported programs have resulted in around 20 million people receiving ART, 25 million lives saved and several countries nearing or achieving new treatment targets. PEPFAR is a great example of a bold, data-driven international initiative that was able to succeed by sustaining local ownership and participation.

Brain Waves Synchronize When People Interact

Scientific American, July 2023

Collective neuroscience, or the study of how brains work together, is a rapidly growing field of research. When people converse or share an experience, they exhibit high degrees of brain synchrony. Researchers are mapping its choreography (rhythm, timing and undulations) to better understand its benefits. Lydia Denworth explains: "Without synchrony and the deeper forms of connection that lie beyond it, we may be at greater risk for mental instability and poor physical health. With synchrony and other levels of neural interaction, humans teach and learn, forge friendships and romances, and cooperate and converse. We are driven to connect, and synchrony is one way our brains help us do it."

How Plastics Are Poisoning Us

The New Yorker, June 2023

To preserve elephants, tortoises and coral, celluloid (plastic) was invented in 1865. Now, these same creatures as well as others are threatened by plastic waste. Large pieces pose hazards such as choking and intestinal tract perforation. When plastic degrades, microplastics, smaller than five millimeters, are formed and can both leach and attract chemical carcinogens. Plastic waste is found floating in the Great Pacific Garbage Patch, the Mariana Trench and human placentas. Matt Simon, author of *A Poison Like No Other: How Microplastics Corrupted Our Planet and Our Bodies* says, "So long as we're churning out single-use plastic ... we're trying to drain the tub without turning off the tap. We've got to cut it out."

The Retrievals

Serial Productions and The New York Times, June-July 2023

A five-part podcast narrative series by Susan Burton explores the events unfolding at the Yale Fertility Center where patients experienced excruciating pain during and after a surgical procedure called egg retrieval to be used for in vitro fertilization. The staff members were unaware of the real cause: a nurse stealing fentanyl and replacing it with saline. This series tells the stories told about women's pain, as well as how it is tolerated and interpreted, including the ways in which it may be minimized or dismissed.

AI & Machine Learning in Medicine

NEJM AI, July 2023

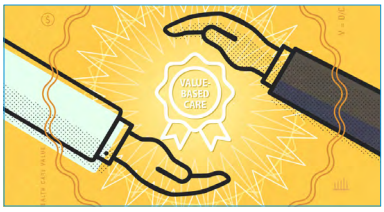
The *NEJM AI* journal editors curated a collection of articles from *NEJM Group* publications exploring the rapid impact and ethical considerations of artificial intelligence (AI) in medicine. The articles cover AI use in clinical applications, imaging interpretation, infectious-disease surveillance, collaborative workflows and real-time diagnostics. The *NEJM AI* journal, set to launch in early 2024, aims to provide a platform for rigorous evidence, resource sharing and thoughtful discussions on AI integration in medicine.

Updates & Events

- On August 4, KFF Executive President for Health Policy Larry Levitt hosted a panel of three experts for a 45-minute discussion of the new weight loss drugs (semaglutide and tirzepatide). Questions discussed included: Who benefits most? Who pays? What are the broader implications for U.S. obesity rates and national health spending? Watch the webinar at bit.ly/KFF-WeightLossDrugs

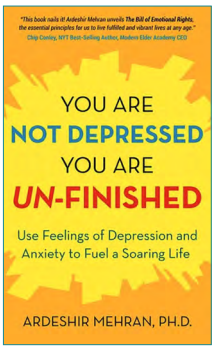
- The STAT 2023 Future Summit will be held virtually from September 5 to 7. The summit will feature executives, global policymakers and patient advocates in discussions on the state of health care, antidotes to the rising cost of care and the future of research and development ushering in a new era of medicine. Speakers include Harvard University geneticist George Church, PhD; BioNTech Co-Founder and CEO Ugur Sahin, MD and AstraZeneca CEO Pascal Soriot. Learn more and register at statnews.com/2023/summit/future-summit

- A free virtual event, Value-Based Care: The Critical Path for Patients, Providers & Payers, will be held by *NEJM Catalyst* on September 13, 2023. Researchers and experts will share why value-based care is an essential, yet difficult, goal to achieve; how to break through barriers to implementation; what is a proper model for payment and how to unlock its potential. Learn more and register at bit.ly/NEJM-VBC-Event



- The 23rd Population Health Colloquium hosted by the Jefferson College of Population Health will offer a hybrid conference and internet event from September 18 to 20 in Philadelphia, PA. This heritage value-based care conference series will gather the most influential people in healthcare transformation. Attendees will gain insights into critical business solutions and discover new approaches on the leading edge of innovation. Chair Billy Oglesby, PhD; Co-Chair David Nash, MD and renowned leaders in health care will be in attendance to share their wealth of knowledge. Learn more and register at populationhealthcolloquium.com

- *You Are Not Depressed. You Are Un-Finished.*, written by a Cura Community member Ardeshir Mehran, PhD, helps individuals analyze their emotions and body to live abundantly. Dr. Mehran shares stories of successful leaders struggling with depression, anxiety, panic attacks and ADHD. His research-based The Bill of Emotional Rights offers lifelong fulfillment boosters for those struggling with these issues. Learn more and order the book at bit.ly/YouAreNotDepressed



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