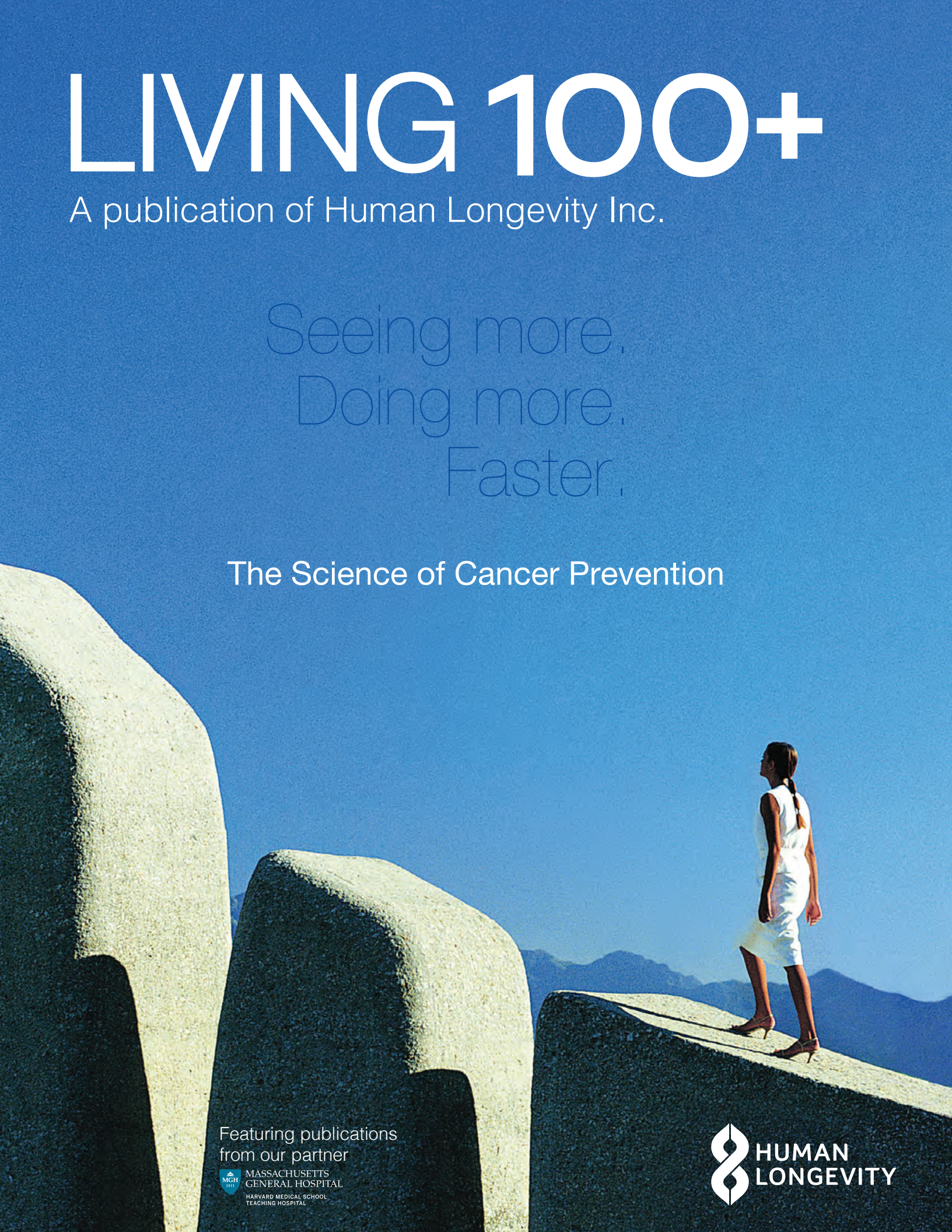
LIVING 100+

A publication of Human Longevity Inc.

Seeing more.
Doing more.
Faster.

The Science of Cancer Prevention



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HUMAN LONGEVITY

Dear LIVING**100+** Reader,

Welcome to the inaugural issue of Human Longevity's quarterly magazine, Living 100+. It is a privilege to have you join us.

Our goal in launching Living 100+ is simple. It is to inform and inspire you to live a long and healthy life.

We plan to help you achieve that goal by providing you with content of the highest quality, including information regarding breakthrough research, diagnostics, and therapeutics from some of the most distinguished minds in science, medicine and technology. To that end we are honored that Massachusetts General Hospital has contributed three compelling articles.

We also want to help you live a long and healthy life by encouraging you to become a member of our new, strategically designed, 100+ longevity and performance membership program delivered by our San Diego and San Francisco-based precision health clinic, Human Longevity. 100+ by Human Longevity is a year-long, renewable, membership program that offers the three pillars of longevity care.

- An annual, data-driven, health check including MRI, whole genome sequencing, blood biomarker and microbiome assessment

- A personally assigned, experienced physician who will design a highly personalized and customized longevity and performance action plan and delivering year-long consultation and care to implement that plan

- Access to world class specialists for second opinion consultation and referral including referral to Massachusetts General Hospital

Join today and take advantage of special introductory pricing by calling client services at 844.838.3322.

My commitment to the science of longevity began when the most beloved person my life died. That person was my grandmother who loved and cared for me when my mother was sent to rural China during the Cultural Revolution. My grandmother died of late-stage cervical cancer at 63, within two months of her diagnosis. The pain and confusion of her sudden death forged my life-long resolve to identify health risk early and fight premature death.

Living 100+ is dedicated to all those who have suffered the exquisite pain of losing a loved one, particularly when such loss could have delayed or prevented. Living 100+ is also dedicated to the thousands of brilliant research scientists, physicians, technologists, entrepreneurs and investors who are tirelessly driving the precision health, precision medicine and longevity movements.

Wei Wu He Ph.D.

Executive Chairman, Human Longevity, Inc.

Introducing 100+, an exclusive precision health program where your own dedicated team of world-class physicians monitor your risk factors based on your genomic insights and our annual imaging diagnostics and biomarker analysis. With technology and science, we detect your health risks early and develop a data-driven personalized plan so you live longer and healthier.

HUMAN LONGEVITY

Everyone ages, but how you age depends on your unique combination of inherited traits and how you live your life.

Welcome to LIVING100+

In this time when our daily lives are still threatened by a world-wide pandemic, it may be tempting to let go of long-term goals and focus solely on the day-to-day challenges. However, I would argue it is even more important today to focus on long-term health. People are still at risk for the same diseases they faced before a novel virus arrived at our doorsteps. The lifestyle choices you make today will affect both your body's response to COVID-19 should you become infected, and your long-term health after this viral threat has dissipated. Shouldn't you take time to make sure you're doing everything you can to keep yourself healthy no matter what comes your way?

Everyone ages, but how you age depends on your unique combination of inherited traits and how you live your life. Here at Human Longevity, our mission is to help you live your longest healthiest life, through early detection, genetic information, lifestyle insights nd management before significant health problems threaten your life.

Using our proprietary data-driven program, we can provide you with insights into your current state of health. We complement this with a comprehensive analysis of your genetic profile to evaluate your current and future risk for disease. Our team of physicians then work with you to achieve your longevity goals.

We hope this publication will inspire you to live a longer healthier life.

Natalie M Schenker-Ahmed, PhD
Editor-in-Chief

CONTRIBUTORS

Evelyn Bischof, MD
Pamila Brar, MD
C Thomas Caskey, MD, FACP, FACMG, FRSC
Hyun-Kyung Chung, PhD
Robert Dinenberg, MD
Keegan Duchicela, MD
Mona Ezzat-Velinov, MD
Wei-Wu He, PhD
Robyn Heister, MD
David S Karow, MD, PhD
Brissa Martin, MS
Natalie M Schenker-Ahmed, PhD
Emily Smith, MS
Keith Vaux, MD
Hai Yan, MD, PhD

GUEST CONTRIBUTORS

Jeffery Brown, MM
Kay Cahill
Lauren Carr
Nick Engerer, PhD
Daniel Haber, MD, PhD
Constance Lehman, MD, PhD
David Miyamoto, MD, PhD
Joseph Nevin, MS
Lecia Sequist, MD, MPH
David Ting, MD

4570 EXECUTIVE DRIVE
SUITE 100
SAN DIEGO, CA 92121

844.838.3322

HUMAN LONGEVITY

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What is Cancer?

By Natalie M Schenker-Ahmed, PhD

Cancer refers to malignant tumors, or cells that exhibit abnormal growth and have the potential to invade or spread to other regions in the body. This is in contrast to benign tumors which may show abnormal growth, but do not spread.

Hallmarks of cancer:
Self-stimulated growth:
Usually cells are "told" to multiply by signals coming from elsewhere in the body. Cancer cells reject this and will continue to undergo cell division without external input..

Insensitivity to external anti-growth signals:
Healthy cells have checks and balances that prevent uncontrolled growth. These processes do not function normally, allowing cancer cells to grow unchecked.

Evading detection and "programmed cell death":
Normal cells have a mechanism by which they are programmed to self-destruct if they become damaged. This mechanism is characteristically absent in cancer cells.

Limitless reproduction:
Normal cells have a reproductive lifespan, i.e. they can only divide a set number of times before they die. Cancer cells are apparently capable of infinite growth and division.

"Sustained angiogenesis":
Cancer cells can trigger the body to generate new blood vessels that sustain the cancer with oxygen and nutrients.

Invasiveness and metastasis:
Cancer cells can break away from their site of origin to invade surrounding tissue or to spread to distant parts of the body.

Hanahan, Douglas, and Robert A. Weinberg. "The Hallmarks of Cancer." Cell, vol. 100, no. 1, Elsevier, 7 Jan. 2000, pp. 57–70, doi:10.1016/S0092-8674(00)81683-9.

How common is cancer?

Over 30% of women and close to 50% of men will have a cancer diagnosis in their lifetimes. In 2020, close to 1.8 million new cancer cases will be diagnosed in the United States. The most common cancer is breast cancer, affecting nearly 280,000 people with 99% of cases being in women. The next most common cancer is lung cancer, affecting men and women equally, followed by prostate cancer, exclusively in men. Over 600,000 people will die of cancer in 2020, with the leading cause being lung cancer, followed distantly by colorectal cancer and pancreatic cancer.

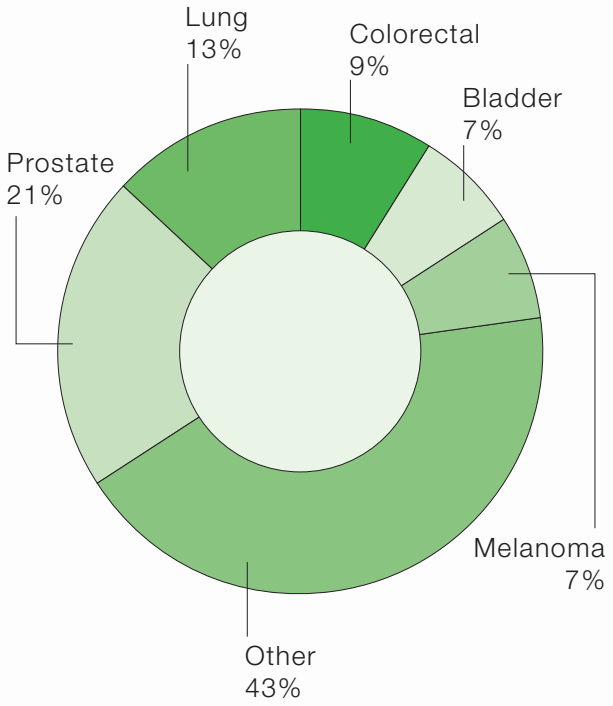
What affects my risk of getting cancer?

Cancer risk is linked to a variety of causes, including lifestyle factors; exposure to physical or chemical agents; exposure to certain pathogens; radiation exposure; and genetics. Hereditary cancers make up less than 10% of all cancer cases. In fact, over 4 in 10 cancer cases are preventable! Maintaining a healthy lifestyle and limiting environmental exposure to cancer causing agents, like those found in tobacco products, can drastically reduce most people's risk for developing cancer.

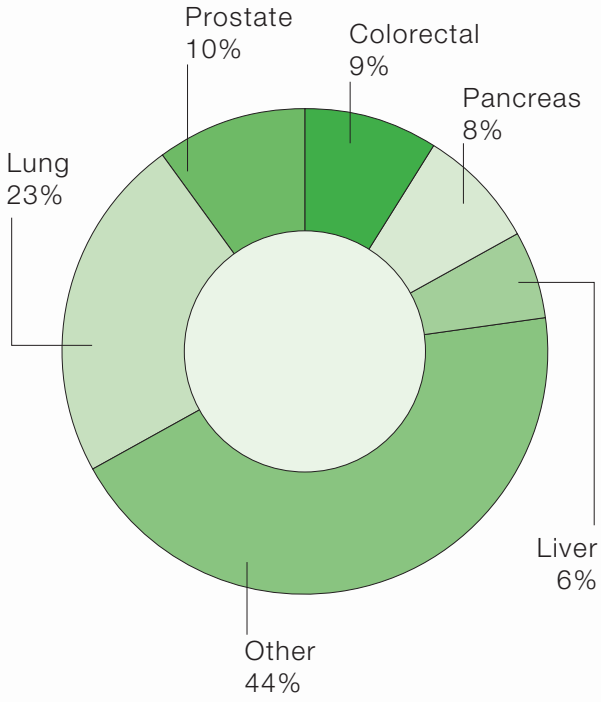
What if I still get cancer?

Getting early and regular screening for cancer can enable early detection of malignancies. The earlier a cancer is detected the more likely it is that it can be treated definitively and grant you more years of disease-free living. If you have had genetic testing, your doctors may be able to identify personalized treatments for you that will do the best job of removing your cancer. And your 100+ physician will be with you along the way to make sure you receive the proper treatment and care.

TOP CANCER DIAGNOSES IN MEN

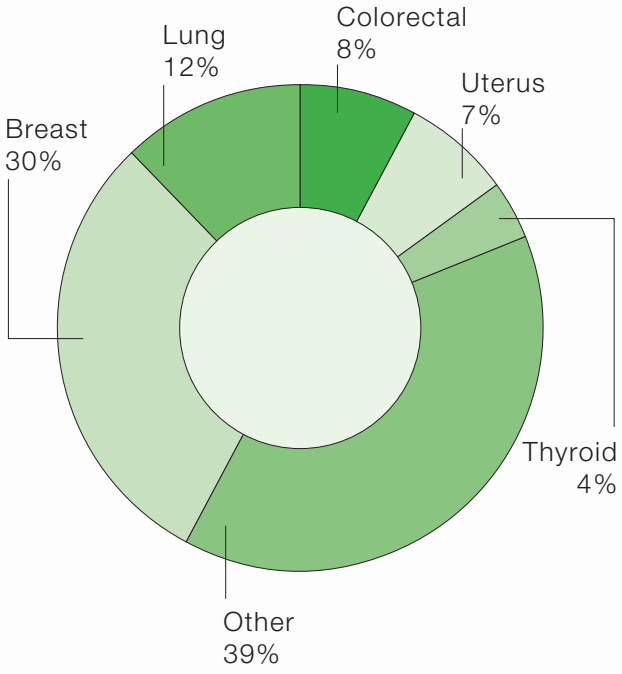


TOP CAUSES CANCER DEATH IN MEN

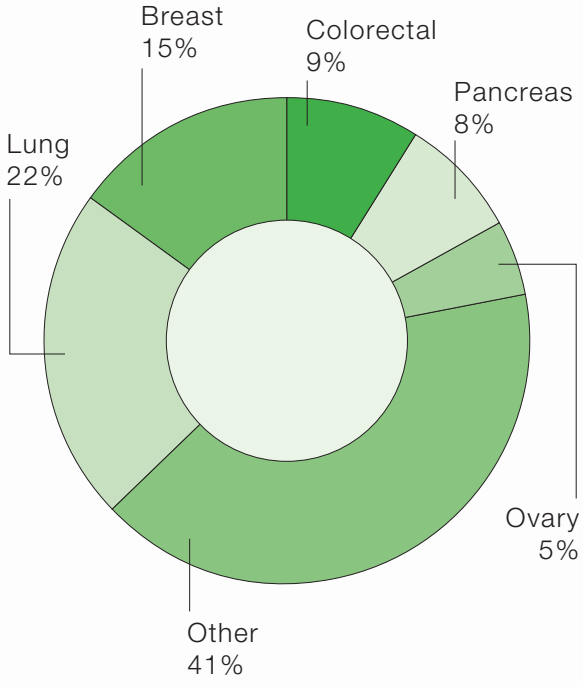


Over 30% of women and nearly 50% of men will have a cancer diagnosis in their lifetimes. In 2020, close to 1.8 million new cancer cases will be diagnosed in the United States.

TOP CANCER DIAGNOSES IN WOMEN



TOP CAUSES CANCER DEATH IN WOMEN



Data from the American Cancer Society's Cancer Facts & Figures 2020: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf

Preventing Cancer Through Lifestyle

By Mona Ezzat-Velinov, MD

In 1924, Otto Warburg described a phenomenon in which cancer cells developed a different method of generating energy. He proposed that cancer cells rely primarily on the fermentation of sugar rather than using oxygen and aerobic respiration to produce energy. This process is now called the Warburg effect, in which nearly all tumors take in large amounts of glucose and release lactate. Malfunctioning mitochondria are the culprits for this alteration in energy production, which results in increased growth and decreased rate of cellular death. Warburg's theory lost popularity for years but was revived in the 1970's by Peter Pedersen PhD, of John's Hopkins University. Since then, numerous studies have investigated ways in which cancer is affected by lifestyle. Here we explore what is now known and consider certain diets which may help to reduce your overall risk of this all-too-common disease.

The Exposome

In health, as well as disease, it is not one single thing that determines how we are, but a combination of multiple factors. The exposome has been defined as the totality of exposure individuals experience over their lives and how those exposures affect health. We will discuss nutrition in a moment, but first let us consider an individual's exposome beyond diet, including such things as environmental exposure, hormone balance, medications, body composition, amount of daily physical activity and any underlying inflammation.[1] Each element exerts influences on health and risk of disease independently and through interaction with other elements. For example, inflammation is a known risk factor for cancer as it is for other diseases. To reduce cancer risk, we can target chronic inflammation by moving to eliminate inflammatory triggers and also support the body so that it can remove inflammation causing substrates in the body.

Chronic inflammation is further triggered by two conditions directly related to diet and nutrition. Obesity and metabolic syndrome are often the result of a diet of sugar and highly processed foods, combined with poorly managed stress and lack of sleep. These all combine to systematically increase insulin levels in the body. This is fertile ground to cultivate adipocytes, which are the fat cells. Adipocytes are not just storage tanks for fat, but also act as an active endocrine organ that secretes cytokines and hormones that trigger chronic inflammation.[2] Increased inflammation leads to local tissue damage, which, like a local wound,[3] induces an influx of immune cells and growth factors, and triggers tissue remodeling and new blood flow to the area. The resulting microenvironment provides tumor cells everything they need to grow to take over the mechanisms to support their own growth and tissue invasion.[4] To stop this process of chronic inflammation at the source, we must address diet, as well as sleep and stress. The basic tenets for keeping inflammation in check include meditation, movement, proper sleep, and a proper diet.

Mediterranean lifestyle

One of the most often evaluated diets for cancer, as well as heart disease and overall weight balance, is the Mediterranean diet. This diet includes a variety of vegetables as its base, with an emphasis on consuming locally and seasonally available options.

The pyramid for the Mediterranean diet has as its foundation physical activity and community activity[5]. Every meal should be dominated by vegetables (2 or more servings per meal) and whole grains (1-2 servings per meal), with fruit primarily as dessert (1-2 servings per meal). Also included are olives, nuts and seeds (1-2 servings a day) and dairy on a daily basis. On a weekly basis, is included a variety of protein from fish/seafood (1-2 servings per week), eggs (2-4 servings) and poultry (2 servings), while limiting red meat and processed meat consumption. Again, the focus is on whole foods and any sweets or alcohol are to be included only in moderation.

The fiber content of this type of diet supports the growth of good bacteria in the gut microbiome and increases the production of short chain fatty acids, which have been linked to reduced risk of inflammatory diseases, diabetes, and cardiovascular disease. The emphasis on a variety of colors of vegetables and fruits provides added benefits from the intake of a broad range of micronutrients and phytochemicals. Phytonutrients are both antioxidant and anti-inflammatory, which means they can reduce the effects of free radicals and inflammatory triggers in the body.[1] A build-up of free radicals in cells may otherwise cause damage to DNA, RNA and proteins, and potentially result in cell death.[6]

Ketogenic diet

Another diet that may be beneficial in prevention and treatment of cancer is the ketogenic diet. This diet was originally developed in the 1920s to treat epilepsy in children. It was used for two decades as a therapeutic option until drugs were developed to treat this condition. The current epidemic of obesity and cancer in America has renewed interest in the ketogenic diet. This diet has helped many lose weight, but it may not be appropriate for everyone and is not necessarily considered ideal as a long-term solution.

The ketogenic diet may also serve a therapeutic purpose when incorporated into cancer treatment regimens. Miriam Kalamian's book Keto for Cancer assists patients and their families to get started on the ketogenic diet as an adjunct to conventional treatment. The idea with a keto style diet is that you can decrease the amount of glucose available to the cancer cells while maintaining a steady supply of energy from beta hydroxybutyrate, a ketone body, and thereby induce apoptosis (cell directed death) in unhealthy cells. This diet can help sensitize tumor cells to standard-of-care treatments and increase the overall success of those treatments in clearing some tumors.[7] Recent studies of the use of the ketogenic diet in glioma cases indicate that not only does the ketogenic diet affect the cancer cells, it also induces genetic and immune changes which benefit overall wellness.[8] The ketogenic diet also modulates oxidative stress and reduces the chemicals in the body that trigger inflammation. In general, it seems that a ketogenic diet provides added support to cancer patients and can also be a way to decrease cancer risk overall.

Fasting

Fasting has been a part of various cultures for centuries and is now entering the mainstream. When you fast, your gut and liver are given time to clear out by-products of digestion and clear the inflammatory process that happens when we eat. It also enables the body to tap into stored fat to use for energy. Further, adaptation to starvation requires the body to divert energy into various protective systems in order to minimize the damage that might come from starvation. It is thought that by triggering these systems, fasting can also increase longevity and decrease cancer risk. Fasting may also protect cancer patients against the harmful side effects of cancer treatments. As long as there is no chronic weight loss, fasting for up to five days, followed by a normal diet prior to treatment may reduce side effects from treatment, without interfering with the beneficial treatment effects. For general cancer prevention, it may be helpful to add intermittent fasting (at least 13 hours without food) to a colorful plant-based diet like the Mediterranean diet discussed above.

The paradigm of cancer prevention and treatment is changing. It is becoming clear that there is much we can do in our day-to-day lives to support our health and avoid receiving a cancer diagnosis.

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EXPOSOME

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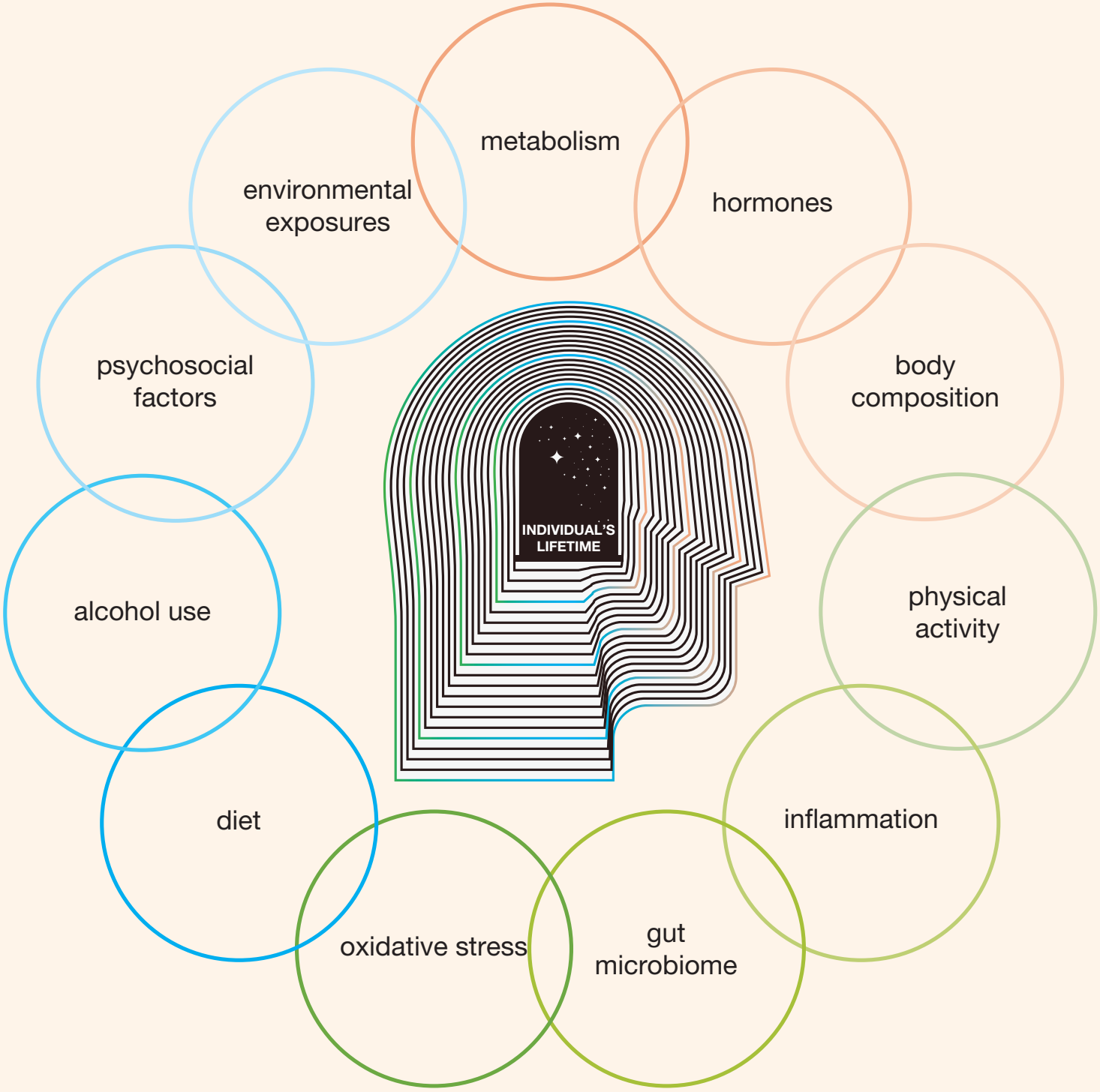

Modified from: Mentella, Maria Chiara, et al. "Cancer and Mediterranean Diet: A Review." Nutrients, vol. 11, no. 9, MDPI AG, Sept. 2019, doi:10.3390/nu11092059.

Functional Medicine and Cancer Prevention and Treatment: An Interview with Dr. Mona Ezzat, MD, ABFM, ABIHM, IFMCP

As a physician at Human Longevity, I believe health can flourish throughout our lifetime. From the microbiome to brain health, our daily habits connect all of our systems to one amazing network.

What is functional medicine?

Functional medicine is a systems biology-based approach to medicine. Fundamentally, this approach incorporates a deep evaluation of how the body works, and how the different parts of the body integrate to work together.

What role can functional medicine play in preventing or treating cancer?

Functional medicine can help treat a patient with higher risk for developing cancer by reducing their environmental exposures. Reduction in environmental risks will help to protect the body from DNA damage. Food and supplements can be used to activate healing mechanisms within the body. Food can also be used to drive healing and optimize the gut bacteria.

One of the main ways functional medicine approaches cancer prevention and treatment is through making sure that the body's natural detoxification pathways are working properly. If the body isn't removing toxins adequately, those elements are likely to result in mutations that are more likely to lead to cancer. Supporting detoxification means balancing stresses to the body with repair mechanisms. One significant stress can be a poor diet, so fixing a patient's diet can reduce their risk of developing cancer. The exact way in which this is done may vary depending on what particular risks a patient has, however, in general, the best advice is to eat whole foods, to avoid processed foods, and to avoid sugar. Eating whole foods and eating a colorful diet that includes a wide variety of phytonutrients is important to help the body detoxify and cope with various types of exposures. One of the best ways to ensure you have even variety is to have at least three colors of food on your plate at each meal.

How do you treat a client with cancer?

For treating cancer, functional medicine's primary role is supporting the body as the patient is undergoing treatment. First, it is important to address the mind/body connection. A cancer diagnosis produces a lot of emotions. A patient needs to be supported and counseled to help them work through those emotions. Following that, I would again work on nutritional support. A lot of patients are told to eat whatever they want so they don't lose weight during treatment, but that means many patients eat a lot of sugar. Eating sugar is the worst thing you can do if you are trying to rid yourself of cancer, because tumor cells thrive on sugar. My approach would be to help a patient develop a foundation of nutritious food that they can tolerate even with the potential gastrointestinal side effects of treatment. That foundation would involve helping them get family or other support to help them to prepare foods to get their nutrients as easily as possible. Next, a patient may require additional supplement support depending on what they are being treated for and how they are being treated. Beyond that, contrary to the idea that patients should eat whatever they want, there is a lot of research surrounding fasting and chemotherapy and how fasting may improve the results of chemotherapy while also protecting healthy cells from being damaged.

We can also change a patient's diet to alter the environment for the tumor. For instance, we have a patient with an early low-grade case of prostate cancer. Under a standard-of-care model he would have been placed on active surveillance where his condition was monitored on a regular basis until the cancer became high enough grade to trigger further treatment. However, under our care, we have also given him a plan to reduce the possible food triggers in his diet. We removed dairy and moved him to more of a vegetable plant-based diet. While this diet is designed to help him combat the cancer, it has also resulted in significant healthy weight loss. When he came back to the clinic for follow-up imaging, his prostate lesion showed some signs of reversing, with less significant signal in the MRI!

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What if a patient is a high risk for cancer?

First, we would focus on finding the risk factor that is most critical for them, and work on reducing that risk as much as possible. Each type of cancer might require a slightly different program. For example, if we have a patient who has a genetic variant that puts them at increased risk for breast cancer, we advise them to consume a diet that helps their body to detoxify estrogen. This would mean cruciferous vegetables such as broccoli, cauliflower, and other sulfur-rich plants. Broccoli sprouts also contain sulforaphane, which helps to detoxify estrogen specifically. Then we try to make sure that the gut bacteria are in balance by including a lot of fiber in your diet, and flaxseed can also be helpful to rebalance hormones. In addition to diet, we would also work on stress management, because when you get too stressed you make cortisol instead of progesterone, leading you to become more estrogen dominant. And finally, encouraging healthy sleep, because sleep is important for the detoxification pathways as well as keeping hormones in balance. Beyond these basic guidelines, we would want to do additional testing to see the levels of certain biomarkers in a particular patient, and then we could tailor the guidance to keep those markers in the right range.

What drives you?

My motivation started with my own health which was compromised when I went through cancer. I was diagnosed with thyroid cancer out of the blue. I had a small lump in my neck and had an ultrasound to assess. There was some calcium deposit, and so a week later I had it biopsied. It came back as thyroid cancer, but no one could tell me where it came from or why it was showing up. I had surgery a couple of weeks later, followed by radioactive iodine. I was not warned or counseled about side effects. The iodine messed up my gut horribly, which I was not prepared for. Also, despite being young, I was not counseled about the possible effects of the radiation therapy on my fertility. I went to a gastrointestinal specialist who could not diagnose my digestive problems and simply tried to treat it with medication.

Fortunately, I had started to learn about functional medicine at an integrative medicine conference in San Diego the weekend after I received my diagnosis. I saw a nutritionist who performed a gut microbiome test for me, and my microbiome was a mess. He also measured my stress levels which were off the charts. So, I had to work on both my diet to help fix my gut microbiome and my self-care to reduce my stress levels. When I was diagnosed, I would go to work and see patients all day without any break, not even for lunch, and then I would have to file all of the paperwork and the other things a physician has to do. I had to learn how to take care of myself, how to find balance, and how to slow down, and change my diet and nutrition. It's been a really big evolution for me, in many ways. I have had to learn a lot more about how my body works and what is necessary for me to be healthy. For instance, I've learned better ways to help my body detoxify, including regular exercise and much more meditation that I ever did in the past. In some ways, the cancer diagnosis was a blessing in disguise, because it forced me to make personal shifts in so many different ways. And it also drove me to really learn about functional medicine, leading me to become a certified practitioner in 2019. Now, I can use everything I've learned to really help my patients to combat and prevent cancer and live longer, healthier lives.

100+ is my ideal partner in my endeavor to preserve health.

Nick Engerer, biohacker and longevity blogger, shares his 100+ experience..

I was directly confronted with mortality in a unique and profound way, when my wife was diagnosed with a rare cancer of the appendix during the birth of our son. Since my wife's diagnosis with cancer in 2013, I've been at her side through two multi-week hospital stays, followed by months of recovery from major surgery. As if that wasn't harrowing enough, two of my closest friends received advanced stage cancer diagnoses in the same year. All three of these people were in their late 20s.

Thankfully, due to the capabilities of modern medicine, my wife and friends are alive and well today, but those outcomes were far from certain. These experiences imprinted upon me an acute awareness of the relative fragility and uncertainty of life. Nothing has been more powerful in motivating me to do everything I can to preserve my health. Once you've lost your health, nothing else matters, and there is no guarantee you'll fight your way back. For me, these experiences were a call to stay as strong, robust and healthy as I could, and make the most of the time I have.

The Human Longevity attracted my attention through a co-founder of Human Longevity Inc, Peter Diamandis. As a member of his A360 program, I was offered partial sponsorship to experience 100+ care. As a technology enthusiast with a newfound zest for staying alive, the value of a service which can fully analyze your health trajectory excited me. I immediately signed on and had my first visit in May 2018.

Before I came to 100+ at the age of 32, I'd only experienced traditional 'reactive' health care. I would have a specific complaint or illness, visit a doctor for 10 minutes, and go home with a treatment to implement over the next few days. My experience with 100+ could not have been more different. I came with no specific complaints, spent more than 2 hours with a diverse team of medical professionals and came away with a reinvigorated lifestyle to implement—not over a few days, but for the rest of my life!

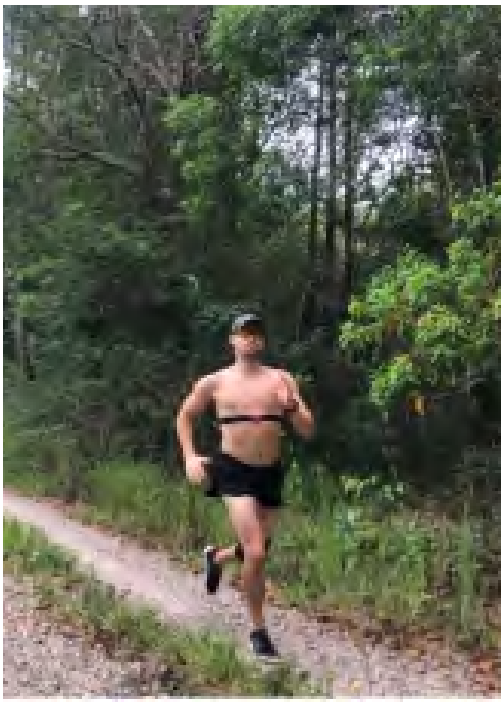
When I arrived, the warm welcome from the highly professional staff and the escort to my private suite for the day gave the excellent feeling of being the 'center of attention'. And of course, to the team of medical professionals reviewing my body in detail, I was! In my complimentary grippy 'Human Longevity' socks, and a made-to-order coffee in my hand, I felt relaxed and safe, despite feeling some nervousness about what might be discovered.

I interacted with several types of healthcare technology throughout the day, but the 70 minutes in the MRI machine was what left the most lasting impression. As the radiation-free electro-magnetic machine scanned my body from head to toe, I felt elated. What an amazing feat of technology surrounded me, mapping the entirety of organs, tissues, bones and more in great detail. It was perhaps the most 'futuristic' thing I have ever experienced.

I learned a wealth of information about myself at many different levels, from the genome, to the detailed look inside my body, and the comprehensive blood panel. From this emerged a clear need for me to be more active. While I was at a healthy weight, eating a whole foods-based diet and relatively 'fit' in my own mind, that's not what the data

showed. There was a clear lifestyle change required of me by 100+- namely at least 30 minutes of vigorous physical activity a few times a week, in order to improve my blood pressure, blood lipids and overall health outlook.

On the day of my visit, my doctor had encouraged me to exercise more vigorously and more often, to improve several of my risk factors. It was something I'd heard before, but despite hearing the 'you should exercise more' line yet again, this time it stuck. I had not come all the way to San Diego (from Australia) to partake in the world's most advanced proactive healthcare to not listen to the doctor's instructions. In the weeks following my visit, I took it upon myself to make a lifestyle change, sweating out a newfound aerobic fitness habit 4-5 days a week, just as she had instructed. One of my favorite moments in my follow-up care experience was during the long form call with the doctor to review all of my results. The smile on her face and happy laugh when I shared this change during that call is a moment I won't soon forget - imagine having your doctors cheer for you and your longevity. It's a great feeling! Today, at 35 years old, I'm in the best shape of my life, having gone well beyond 30 minutes a few times a week, to winning 5K races, lifting weights, and training for my first Olympic triathlon later this year. I could not be more grateful for the impetus given me to 'upgrade' my longevity strategy and stay fit for life!



As part of that lifelong strategy, I will be returning every 12-18 months for a repeat trip to 100+. Full-body disease screening, particularly cancer, is now a pillar of my longevity strategy. I'm no longer contented to leave my health 'up to chance', for as the experiences of my wife and friends demonstrated, even young people are not immune. As a part of that longevity strategy, I aim to minimize my mortality risk with long-term thinking and risk management. Early detection of disease, particularly cancer, leads to great improvement in prognosis. 100+ now makes that possible.

Also, as a newly minted fitness enthusiast, I am fascinated by the level of detail the full body MRI offers in terms of body metrics. 100+ data has helped me to see the difference my new lifestyle has made, from the inside out. Not only have my blood pressure, lipid profile and metabolic health all improved, but my muscle mass (particularly in the legs) has increased along with my fitness. Using the 100+ MRI data to track my performance intrigues me, and I am trying to improve my body composition with each visit, and I've made it a personal goal to keep growing the muscle mass in my legs over subsequent visits. In my next 100+ check-up, I will also be old enough to take advantage of the cardiac CT scan to take an early look at any signs of cardiovascular disease. Keeping my body strong and my heart healthy are now a top priority!

I am so enthusiastic about my longevity strategy that I've made it part of my life's mission to spread the word about technologies that can help us live healthier longer. I can think of no better partner in that journey than 100+. The staff, physicians, managers, investors - the whole team at Human Longevity Inc, share that mission - it's what gets me up in the morning and working late into the night.

But at the end of the day, the choice on whether or not to be a part of this effort to bring proactive healthcare to the world, lies with you, the reader, personally. Where will you choose to invest your time, energy and resources? If not in ensuring the quality and duration of your life left on this planet, what else? Don't be another 'they found it too late', 'he keeled over dead, heart attack' story - take ownership of your health, manage your risk, look early and look often! Never before have we had a resource like 100+ at our disposal for optimizing our health and preventing late-stage disease diagnoses! Take advantage of it, so you can continue to be here for your loved ones and live a long, healthy life.

He felt healthy and in good condition but his 100+ screening revealed a tumor.

Technology investory, and Silicon Valley insider Jeffrey Brown, shares his very personal journey as a 100+ member in an online series "The Bleeding Edge".

What good is wealth if we don't have our health to enjoy it?

That was the question on my mind last August when I traveled to La Jolla, California, to visit a company called Human Longevity. From my perspective, it's the future of health care.

My research into the longevity movement led me to Human Longevity, San Diego. What an amazing discovery. From my perspective, Human Longevity is the future of health care. There is no place on earth like it, and it is a lens on the future... not only for our health but for the future of the industry. It functions on the bleeding edge of preventive medicine. It's the opposite of what our health care system is today. It doesn't treat our symptoms... it finds them before we have them.

This time, my research was a bit different. Rather than a company or technology being the focus of my attention, the subject was me. I flew to San Diego to put myself through the tests and diagnostics so that I could deeply understand what the future looks like. I was the one being poked and prodded this time. And my crazy idea to do so may very well have saved my life.

I first learned about Human Longevity back in 2014. That's when I noticed an investment made by genetic sequencing giant Illumina into a company called Human Longevity. The mission of Human Longevity was seemingly straightforward: to evaluate the human condition from head to toe (our phenotype) and compare that to a whole genome sequence – an analysis of all 3.2 billion base pairs of our human DNA. By doing so, it is possible to map our genetic structure to our current or future conditions.

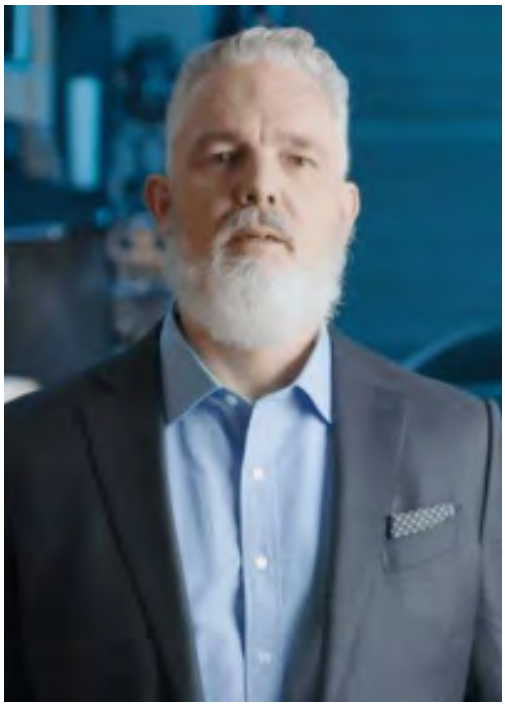
Why is this so invaluable? It empowers us to understand our current and future risk for disease, what kind of medications we will respond well to, and even medications that would have adverse effects on us due to our genetic structure. Knowing these things in advance can be lifesaving. It also empowers us to make adjustments in our lifestyles to avoid a certain "fate" that we otherwise would have been faced with down the road. The mission of Human Longevity and Human Longevity was so compelling to me that I actually visited back in 2015 to research the facility. Knowing what I know now, I regret having not put myself through the Human Longevity 100+ program at that time. Over the last five years, there always seemed to be a scheduling conflict, another business trip, too many balls in the air, and so on to just lock in a date to visit. The experience is incredible, but I'll be the first to admit it is not for everyone.

Blood... lots of blood

I wasn't even sure if I would have enough left to make it through the day.

That's how my day at Human Longevity started. After a fast from the evening before, the first thing that the team needs to do is capture your blood. It is a great way to get a snapshot of what our system looks like on any given day. But this isn't the kind of blood test that our family doctor orders to check in on our cholesterol. It's a completely different approach. Rather than looking for a specific marker that might explain a symptom or checking if we To me, these numbers are remarkable. And they perfectly

have influenza A or B (or COVID-19, for that matter), the team at Human Longevity looks for anything that may reveal something is wrong or even a bit off kilter. More than 40 different blood biomarkers are tested for things like kidney and liver function, insulin sensitivity, glucose levels, a detailed cholesterol panel, biomarkers for inflammation, hormones, vitamins, nutrients, heavy metals, prostate-specific antigen (PSA) values, lipids, and more. The analysis even looked at more than 900 metabolites, which is what is left over after the body has metabolized food – that's one of the reasons why we fast before the blood is drawn. When the results came back, I had nine detailed pages of analysis. And yes, I needed some help to interpret all of the data.



What came next was one of the highlights of my visit, something that I had genuinely been excited about… a full- body magnetic resonance imaging (MRI) scan. This isn't something that we would typically ever do. After all, if we are having terrible shoulder pain and can't lift our arm above our head, the orthopedist orders a shoulder- specific MRI. The doctor will just focus on where the symptom is presenting. At Human Longevity, the goal is to take a very detailed whole- body view to see if anything is of concern. And when I say detailed, I mean it. The typical MRI that most of us experience uses a 1.5 Tesla (1.5 T) machine. A Tesla is the unit of measurement for the strength of the magnetic field of the MRI scanner. But the full-body MRI scan at Human Longevity uses a 3 Tesla scanner. As we can easily discern, the 3 T scanner is twice the strength of the 1.5 T scanner. As a result, it produces incredibly clear images of our bodies.

Worth mentioning is that the MRI scanners are completely safe. In that regard, the 3 T machine is no different than the 1.5 T machine. But the real value comes from the ridiculous level of detail in the images after the MRI scan has been performed. The full-body scan typically takes about 90 minutes – and sometimes more for those who need a break between scans. I definitely benefited from stretching my legs a couple of times during the process.

The imaging starts with an extremely detailed scan of the brain. The resolution enabled the MRI to map out the brain's blood vessels. The scan is capable of finding an aneurysm as small as 3 millimeters in diameter. My wife was convinced that they would find something wrong up there… but I proved her wrong and received a glowing readout on my brain scan. Ha! After the brain, the process is repeated for the cardiovascular system. I'm not kidding when I say that the machine takes the equivalent of a high-definition video of the four chambers of the heart. After the scan has been completed, we can literally see our heart functioning. And, of course, the physicians can determine with remarkable accuracy how well our cardiovascular system is functioning.

Ultimately, the MRI produces a full-body analysis of our body composition. It can "see" how much muscle and fat we are carrying. We can understand with specificity how much subcutaneous fat (the fat visible under our skin) we have. And even more valuable is how much visceral fat we are "hiding" inside. The visceral fat is the fat that surrounds our vital organs. We may not be able to see it, but it is the more dangerous of the two. Too much visceral fat is associated with cardiovascular disease, stroke, diabetes, and inflammation, all of which dramatically weaken our immune systems and even make us susceptible to an airborne virus like COVID-19.

I'd like to mention that my visit to this facility has made clear the investment opportunity in the precision medicine space. Investment trends like genetic sequencing and genetic editing are on the rise. For investors who haven't taken a position, now is the time.

After the full-body MRI, it was time for my computerized axial tomography scan (CAT scan). I remember when we used to call them CAT scans, but these days they tend to be called CT scans. These CT scanners simply take X-ray images from many different angles. Then computers combine these images to create cross sections that allow us to "see" inside the body in a way we couldn't with a normal X-ray. This particular scan looks at the cardiovascular system. More specifically, it is used to measure the amount of calcified plaque in the arteries of our heart. This allows the team to quantify a coronary calcium score, a useful indicator of our cardiovascular health. In short, the more plaque that is found in this scan, the higher our risk is of having a heart attack.

Next up was my echocardiogram and electrocardiogram (EKG), which I'm sure many of us have had done before. The echocardiogram uses ultrasound to measure the size and shape of our heart. When used properly, it can accurately calculate the pumping strength of the left ventricle. It can also detect early signs of heart valve disease and any hypertrophy (thickening) of the heart muscle. The EKG analyzes our heartbeat to determine if it is irregular, too fast or slow. Measuring the electrical energy that travels through our heart is also a useful diagnostic measurement for hypertrophy or fatigue. Any one of these tests can give us a few data points on our cardiovascular health but not the complete picture. That's why Human Longevity collects all of the data from the MRI, the CT scan, the echocardiogram, and the EKG to generate a complete picture of our cardiovascular health. And that's exactly the point. If we don't have a complete picture of our health, we may very well be missing something. And that "something" could be quite serious and materially affect our longevity
.

My last major diagnostic test at Human Longevity in La Jolla, CA, was a bone densitometry scan. This is also known as a DEXA, which stands for dual energy X-ray absorptiometry. DEXA is definitely easier to say. The DEXA is by far the most comfortable diagnostic test that I have ever experienced. It looks just like a bed with a scanner that runs over you from head to toe. The DEXA is able to collect a full "picture" of our body's bone, fat, tissue, and muscle mass. It is a fairly simple and effective tool for diagnosing osteoporosis and our risk for osteoporotic fractures. Obviously, if our bone mineral density is too low, the team at Human Longevity can put a plan in place to improve bone strength and avoid an unwanted outcome. When we combine the output of the DEXA with full-body magnetic resonance imaging (MRI), we really get a clear picture of our muscle mass, bone strength, subcutaneous and visceral fat. And we might even discover something like a fracture that we didn't know existed.

And this brings me to the key point – proactively finding problems with our own health that we never knew about. Consider this: 25% of us who live to 55 will not make it to 75 years of age. I don't know about you, but those aren't odds that I'm comfortable with.And just to be clear, I'm not talking about a death from a car accident or our parachute not opening up. These are deaths from cardiovascular disease, cancer, neurological diseases, respiratory diseases, diabetes, and many other things. But if we know about these factors and our risk, we actually have the ability to create completely different outcomes. That's why the program is called 100+.

Now, if the statistic above didn't catch your attention, I have even more to share with you that will. The teams at Human Longevity and the Human Longevity published some unbelievable research earlier this year. The work is titled "Precision medicine integrating whole- genome sequencing, comprehensive metabolomics, and advanced imaging." This research was years in the making. It analyzed the results from 1,190 adults who went through the same testing that I did... and here is what they found:

- 17% had a rare genetic mutation that affects their health
- 7% discovered they had moderate-to-severe cardiovascular risk
- 28% had elevated liver fat, which was mostly non-alcoholic fatty liver disease
- 2.5% discovered they had body or brain aneurysms
- 1.7% discovered that they had cancer

And at a higher level:

- 14.4% discovered major health issues that were actionable, let's think about that. Out of 1,000 people, 144 found major health problems they didn't know about
- And 40%, or 400 out of 1,000 discovered things that required medical attention or regular monitoring but weren't yet life threatening

explain why one out of every four adults who reach 55 never make it to 75. We simply don't know what's wrong. And if we don't know, we can't take positive actions to heal ourselves. And this is precisely what is broken with the world's current, conventional methodology for practicing medicine. Ironically, treating symptoms as we do today ("sick care") is far more expensive and costs many more lives than the kind of bleeding-edge approach taken by the Human Longevity.

There was a dark blob on the MRI scan.

And as I've been sharing, my experience with Human Longevity has convinced me more than ever in the potential of precision medicine and biotechnology. And there it was... Like a beacon, I didn't need any training to see it. An ominous, dark blob on my magnetic imaging resonance (MRI) scan in the area of my pelvis. Cancer. I was in the 1.7%.

I sat down with Dr. David Karow, the president and chief of radiology at Human Longevity, at the end of my visit. He walked me through the first pass of imaging taken throughout the day. The lesion found during the MRI indicated a high likelihood of prostate cancer. Dr. Karow was certain of it, and he was right. It wasn't what I expected. After all, my trip to Human Longevity wasn't because I was ill. In fact, I didn't have a single health concern before my trip to La Jolla. My goal was to put myself through the process so that I could research bleeding-edge approaches to predictive medicine, genetics, and human longevity.

I'm young, active, and train three or four times a week. I'm strong, energetic, and a third-degree blackbelt in Shotokan karate. I consume a gluten-free version of a largely Japanese-style diet full of fish and vegetables. It just didn't make sense at all. And that's precisely the point of the Human Longevity program. There was no reason to justify me getting a full-body MRI or even a prostate-specific MRI. The cancer would have likely gone unnoticed for years, and it could have potentially cost me my life. As Dr. Karow walked me through the specifics, the natural thing that came to mind was, "Okay, what's next"?

It's disheartening to know that there will be a raft of tests, biopsies, blood tests, and hospital visits to follow. But it is also an empowering feeling, knowing that there are positive actions to create a better outcome. And the great news is that we found the cancer early. My visit to Human Longevity was in the first week of August 2020. Needless to say, I have been very busy managing my health since then. But what happened after I left Human Longevity is equally important to share. Dr. Karow and I agreed that we needed to get a prostate- specific MRI as soon as possible. That would provide the imaging necessary for a biopsy. With his help, we identified a urologist not far from where I lived who specializes in MRI/Ultrasound fusion biopsy, which uses MRI images to help guide where the samples are taken. When used properly, this technique improves the odds that the cancerous tissue is taken from the lesion during the biopsy. When I first met with the urologist, I was told that it was "highly unlikely" that I had prostate cancer. It was a tense discussion, and I had to push to get the support to authorize a prostate-specific MRI. At the time, a biopsy was out of the question.

It wasn't a surprise to me when the prostate MRI came back confirming what we found at Human Longevity, which resulted in a biopsy. And the biopsy confirmed what we already knew back in August. I'm sharing these details with you because I want to demonstrate that we must take ownership of our own health. If I had listened to the urologist – one of the best in his field– that it was "highly unlikely" I was sick and that we should just monitor the situation over time, the cancer would have had the chance to spread, grow, and potentially expand to my bones. That's when things get really ugly.

It's not easy to push back when we believe that we're sitting down with an expert. But with the support of Dr. Karow, who even got on the phone to push for earlier appointments and tests, I was able to avoid a common trap of conventional medicine – that my symptoms weren't significant enough to warrant attention.

And there's more... My other partner through this whole process has been Dr. Mona Ezzat-Velinov, a specialist in integrative and functional medicine. She took all of the data that we collected at Human Longevity and combined it with the additional diagnostics we performed after I left to understand my entire health condition. With her help, I've stripped out any and all foods that have even a remote link to prostate cancer. Since my visit, I haven't had any dairy products, gluten, beef, pork, lamb, and almost zero processed sugar. I call it my "bird diet." I subsist on nuts, seeds, seaweed, fish, copious amounts of vegetables, and herbal tea throughout the day.

Why so extreme? Because I want to get better. I have a family that needs me. And if I have a shot at eradicating the cancer and beating it with nutrition, diet, and exercise, then it is worth the effort. If at all possible, I want to avoid a radical surgery or radiation of any kind. The funny part is that I felt good when I went to Human Longevity, but I feel even better now. I've lost almost 30 pounds in less than three months. It hasn't been easy, but I need to reduce my visceral fat quickly. One way or another, I'm confident that I'm going to be fine. I didn't miss any work through this whole mess either. As long as I had something scheduled that would help us understand my condition better, then work was a welcome distraction. And with clear dietary and weight goals, I have something that I can aggressively work toward.

I'm grateful to Dr. David Karow and Dr. Mona Ezzat-Velinov for being such great partners through this process. The Human Longevity 100+ program is like nothing else on the planet – clearly, I've experienced the value myself. And we need it to succeed in its mission if we are to change the way that health care works today. I wish the program were more accessible, but I am certain that, over time, access to this kind of preventative health care will increase significantly and eventually become the standard.

And thanks to all of you who have read along with me on my journey. You have shared one of your most valuable assets – your time – which is why I have chosen to share my experience with you. And if I could wish one thing for my readers, it's that you all live in good health to 100+.

"You are on the bleeding edge now.. you are the science."

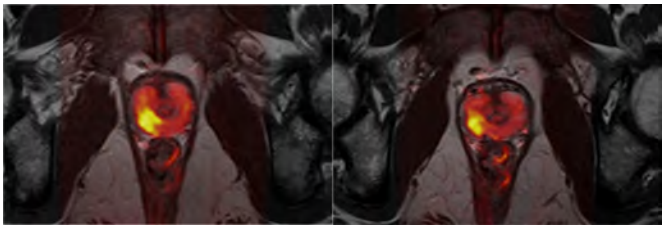
It wasn't what I was expecting to hear, but I couldn't have imagined hearing anything better. I had returned to Human Longevity for my six-month checkup after discovering I had prostate cancer during what I thought would be just a very detailed, routine health checkup last August. Last year, I traveled to La Jolla, CA, to the world's leading center for preventative medicine and human longevity, Human Longevity. I simply wanted to research the bleeding edge of health care. So I thought the best way to learn was to actually go through the process myself. It was a way to see and understand the future of health care and human longevity.

It has been a humbling experience, and it wasn't at all what I expected. I arrived last August feeling great. I was fit, energetic, and unaware of any health issues of any kind. In fact, I hadn't felt so good in at least a decade. It wasn't until I sat down with Dr. David Karow, President and Chief of Radiology at Human Longevity, after a day of testing that I discovered I wasn't so healthy after all. My liver fat was above 25%. My body mass index (BMI) was 34.2. I had dangerous levels of visceral fat and was likely pre-diabetic. And thanks to Dr. Karow, we discovered that I had prostate cancer. I was shocked. After all, I thought I was too young and healthy to have cancer. Aside from exercising three to four times a week, I rarely ever ate processed foods, only consumed natural and organic foods, mostly stayed away from sugar, and slept well.

But the cancer was visible to the eye. It wasn't up for dispute. It was a dark, ominous blob that didn't look like it belonged. And it set a series of difficult steps in motion...

Assembling my treatment plan

After confirming the diagnosis through a biopsy, I put a plan in place with Dr. Karow and my physician at Human Longevity, Dr. Mona Ezzat-Velinov. Because we found it early, I had the opportunity to attack the cancer using my own immune system. But in order to do so, I had to make radical changes to my diet and exercise routine. Instead of weightlifting and kettlebells, I had to make intense cardiovascular exercise the foundation of my weekly routine. Due to my liver fat and visceral fat levels, I needed to dramatically drop my weight and reduce my visceral fat. The only way that was going to happen was through hard work, several times a week. I chose rowing, as it uses about 86% of all muscles. And for those willing to row hard, it really burns calories. After five months of training, I managed to row 10,000 meters in just 41 minutes and 21 seconds. For those who haven't rowed before, I'll just say this... It's not easy..



August 2020 February 2021

I also radically changed my diet. I stopped eating all gluten, processed sugar, dairy products, and high-glycemic foods. And for the first four months, I cut out any alcohol consumption. I also intermittently fasted every day and reduced my overall caloric intake. I felt great after six months of really hard work and sacrifice. But the truth was that I had been procrastinating my return visit to Human Longevity. And if it wasn't for the persistence of Dr. Ezzat-Velinov, I probably wouldn't have returned in February. I was scared what the tests would show. I knew my lab results would show a dramatic improvement, and that my liver fat and visceral fat had dropped, but I had no idea about the cancer. And the most devastating thought that I had was... After all this sacrifice, what if there was no positive impact on the cancer? In other words, it may have been all for nothing.

Fortunately, that wasn't the case.

Great news from the Human Longevity

I sat down with Dr. Karow and Dr. Ezzat-Velinov after completing my tests. Dr. Karow said, "I have good news and more good news." That was a good way to start. My numbers were fantastic. I dropped my liver fat from above 25% to just 5.2%. They told me they had never seen anyone do that so quickly. My BMI had dropped to a healthy level at 29.7. And I had dropped 4.28 liters of abdominal fat and 45 pounds of weight from my peak. But the incredible news was that the tumor had not grown and, most importantly, the MR imaging biomarker of tumor aggressiveness had actually improved. By making these lifestyle changes, I had actually started the process of reversing the cancer.

When Dr. Karow showed the images to me and explained what had happened, I broke down and cried. It wasn't that I was scared of death. I had just been worried that the cancer would have grown and required more aggressive treatment, which would have unwanted, lifelong consequences. The results were precisely the motivation that I needed to keep fighting it and potentially reverse the cancer entirely. That's why "I am the science" right now. We're trying to prove that with the right lifestyle, nutrition, and exercise, we can empower our bodies to do something remarkable... and ultimately live past 100 in good health.

I continue to focus on further reducing my visceral fat and liver fat, and we're working on improving my gut microbiome. These things are critical to having a strong immune system. And I'm now supplementing my routine with regular infrared sauna therapy. The second six months have been much easier than the first six. My body has adjusted, and the truth is that I feel like I'm in my twenties again. And my mental acuity feels sharper than ever before. And unlike this February, I can't wait to return for my next visit in August. I plan on returning every six months until I have this thing beat. That way, we can make adjustments along the way and show evidence of the impact that my changes are having on reversing the cancer. If I made this much progress in the first six months, I know that I can do so much more.

I've met and heard from many Bleeding Edge readers who have already gone to Human Longevity. It's incredible and motivating to me that so many have taken advantage of this amazing facility, its science, and, of course, the fantastic team there that makes it all happen and stays on the bleeding edge of health and human longevity.

Physician's Comments

When Mr. Brown returned to Human Longevity for follow-up imaging in February 2020, it appeared that his hard work and dedication to a new lifestyle were having the desired effect. His imaging allows us to be cautiously optimistic that the change in lifestyle is enabling his body to detoxify and to remove the cancer supportive environment.

In the imaging from Mr. Brown's August 2020 visit, the tumor in his prostate was classified PIRADS 4, meaning that it was highly suspicious for malignancy. On his return visit in February 2021, on follow up imaging the clients ADC (a marker of tumor aggressiveness) had increased (improved). More follow up and more data will be required to understand the long-term implication of this change and whether, in fact, the cancer progression has been mitigated.

About Jeff Brown and Brownstone Research

Neither I nor Brownstone Research have any relationship at all with Human Longevity. We receive no compensation of any kind for writing about my experience there. I paid full price to go through the program. My only interest was to research what I felt to be the most advanced preventative medicine and human longevity clinic on the planet.

Beating Cancer: Early Detection

The Human Longevity team focuses on the importance of a healthy lifestyle, as this has been shown to reduce the risk of developing certain types of cancers. The next best step to beat cancer is through early detection. Survival rates dramatically improve when a cancer is identified and treated while the disease is still confined to the organ where it originated.

What is early detection?

Early detection is the discovery of a malignant tumor while it is still designated as stage 0 or 1, and it has not spread beyond the organ where it started.

CANCER STAGES

Stage 0: Not used in all forms of cancer. Cancer cells are only found in the top layer of cells within the affected body region.

Stage 1: Abnormal cells begin to clump together and begin expanding beyond the top layer of cells but still remain within the organ of origin.

Stage 2: Cancerous cells have begun to form a tumor within the organ of origin.

Stage 3: Cancerous cells have begun to spread into lymph nodes and other tissues near the organ of origin.

Stage 4: Cancerous cells have spread outside the organ of origin and now are found in an organ elsewhere in the body.

Early Detection Works

Early detection is critical for long-term survival, as illustrated in the accompanying chart. You can see how early detection may increase the patient's chance of survival 5 years after diagnosis more than 10-fold in some types of cancer[1]. Where there is often no effective treatment for late stage cancers[2], early stage tumors may be surgically removed or treated with milder drugs[3], sometimes even in same-day outpatient procedures.

Since 1950, the incidence of cervical cancer has declined 70%, mostly due to the advent of the Pap test, a simple screening test for the detection of abnormal cells that has allowed for the treatment of precancerous conditions. More recently, with the discovery of the human papillomavirus (HPV) and the development of a vaccine, there has been even further reduction in the incidence of cervical cancer[4].

Similarly, early detection has been key in reducing the impact of breast and prostate cancers. Five-year survival for breast- and prostate-cancer patients with early stage disease is 98% and 100%, respectively, and survival rates remain high at 10 years[1,5]. Primarily because of improvements in early detection via mammogram and breast MRI, breast cancer death rates declined 40% between 1989 and 2016. The death rate due to prostate cancer also declined by more than half in the same period as a result of advances in screening (i.e. early detection) and treatment.

However, for many cancers, the likelihood of early detection remains low in general healthcare settings. For instance, over 60% of ovarian cancer cases and over half of new lung cancer cases[2,4] are typically not diagnosed until they have spread. Pancreatic cancer is another cancer that is rarely detected early, because patients are typically asymptomatic until the tumor has become very large or spread to other organs.

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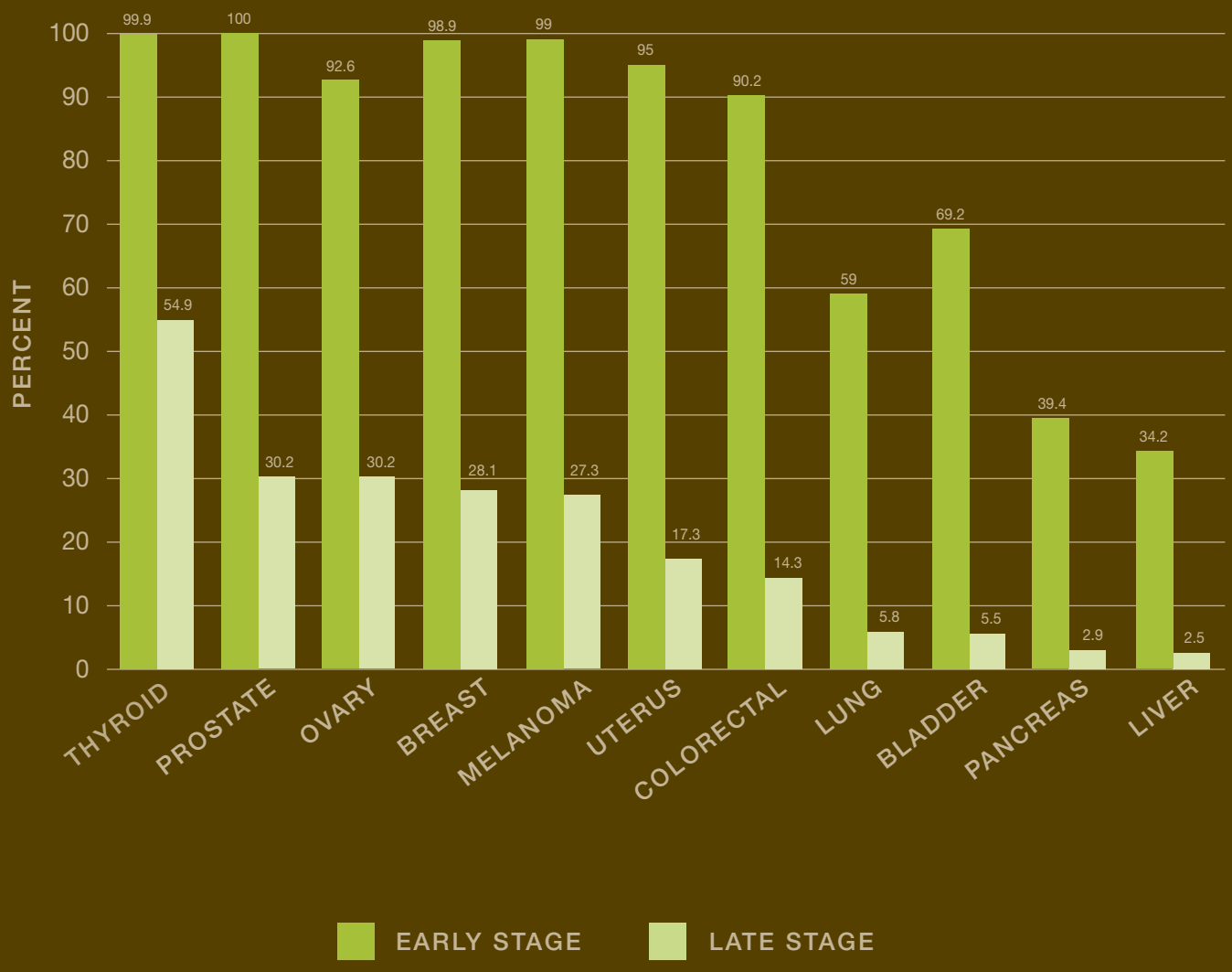
5-YEAR RELATIVE SURVIVAL RATE BY CANCER TYPE



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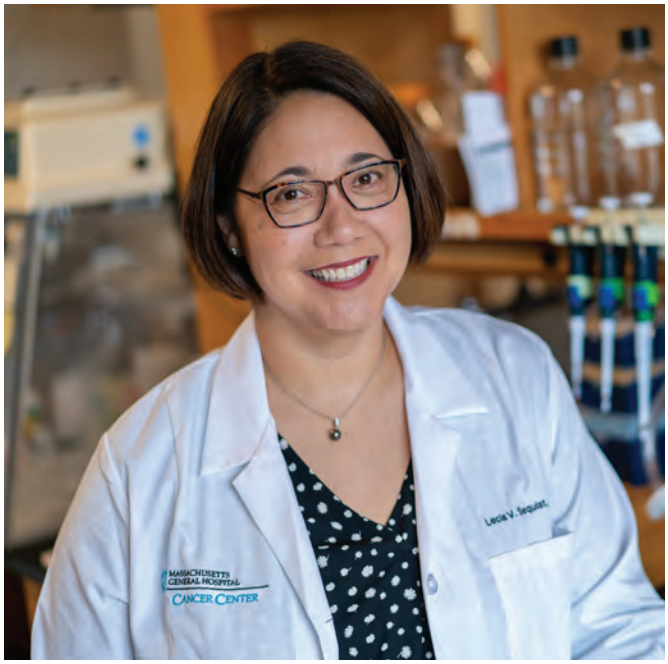
Early Cancer Detection Outlook is Bright

By bringing together patients and innovators, Lecia Sequist, MD, MPH, is advancing the field of early detection to identify cancers earlier, when the chance of cure is greatest.



Lecia Sequist, MD, MPH. Photo by Amanda Kowalski

Lecia Sequist, MD, MPH, is leading the charge for early cancer detection. As director of the Center for Innovation in Early Cancer Detection (CIECD) at Massachusetts General Hospital Cancer Center, Dr. Sequist knows that while new and better cancer treatments are helping many patients, far more would benefit if cancers could be found earlier. That's why she is building a network of cancer researchers, molecular scientists and bioengineers to innovate new cancer detection technologies. She recently discussed the center's work.

What's new in early cancer detection?

The last decade of cancer research has focused on therapeutics — the development of drugs to treat cancers. And that's good. It's made a huge difference in people's lives. But to cure more people, we need to find cancer earlier.

There's a lot of excitement now about developing technologies that detect cancer. It's an important sea change.

There's a lot of excitement now about developing technologies that detect cancer. It's an important sea change. There are only four types of cancer that have a proven screening test. We have mammogram for breast cancer, the Pap test for cervical cancer, colonoscopy for colon cancer and we have a new CT scan for lung cancer. But there are a couple hundred types of cancer. There's so much room for improvement.

Why did you decide to focus on early cancer detection?

I've been an oncologist for quite a while and I mostly see patients with advanced disease. I have to tell a lot of people that, unfortunately, "There's nothing we can do to cure your cancer." We're going to treat it. We're going to fight very hard. But still, when the patient's cancer is metastatic, we still have to say, "I'm sorry, we can't cure you." That's why I decided I wanted to focus on finding new ways to detect cancer earlier when it is more treatable – to help change those conversations in the future.

What is your personal inspiration for this work?

I've seen the difference that early detection can make in my own family. My father was diagnosed with metastatic gall

bladder cancer in his 50s. There is no early screening test for gall bladder cancer. He went through some treatments, but he died relatively young, just after my first child was born.

Then my mother, a couple of years ago, had a routine mammogram. She had breast cancer, but it was caught very early. She was treated with surgery and some hormone pills. She now has a very good prognosis. I see the same kind of story playing out in my lung cancer patients where, thanks to our new CT scan for pulmonary nodules, we're catching lung cancer earlier when it can be successfully treated.

Contributions from philanthropic donors are already helping and we need more.

How is your center, the CIECD, improving early detection?

We're trying to encourage collaborations, to bridge the clinics where our patients are being treated, including healthy patients in primary care, with the researchers who work on early detection. We're also building the infrastructure that will make it easier for these early detection studies to happen. A lot of the existing infrastructure supports clinical trials for drug development. There hasn't been a lot of focus on doing clinical trials for cancer detection.

So, for example, we're setting up a new protocol with the institutional review board (IRB) which reviews research proposals. Typically, the review can take between 6 and 12 months. With this new protocol, if you come to me with a cool new idea and you want to get your hands on some patient samples to test it, we've already got an IRB-approved protocol in place and ready to go. You don't have to start from scratch. Mass General is uniquely positioned to do this because of our location at the epicenter of Boston medical and biotechnology research and our ongoing work with thousands of patients.

What early cancer screening technologies are under development at Mass General?

One of the most accessible types of testing that you can do is blood testing, sometimes called liquid biopsy. It's much easier and less risky than taking a tissue biopsy and you can do it annually and monitor patients over time. For example, we are looking for tumor cells circulating in the blood that can identify cancer. We're also looking at proteins in the blood that provide a kind of fingerprint or evidence that can tell us where a tumor is located and whether it's malignant or benign. We're also looking at urine-based and breath-based diagnostics and we're using artificial intelligence to improve our ability to detect very early cancers through imaging, starting with mammography and CT scans.

How can philanthropy help?

Contributions from philanthropic donors are already helping and we need more. They support the all-important pilot studies that generate the first set of data. It's incredibly hard to get a grant from the National Institutes of Health or elsewhere to cover an idea that hasn't even started yet. Many of our new technologies are under development but we are not yet using them in patients. So, our center helps by providing the philanthropic funding needed to move forward these early cancer detection pilot studies.

Contact us via email at mghdevelopment@partners.org or call us at 617.726.2200

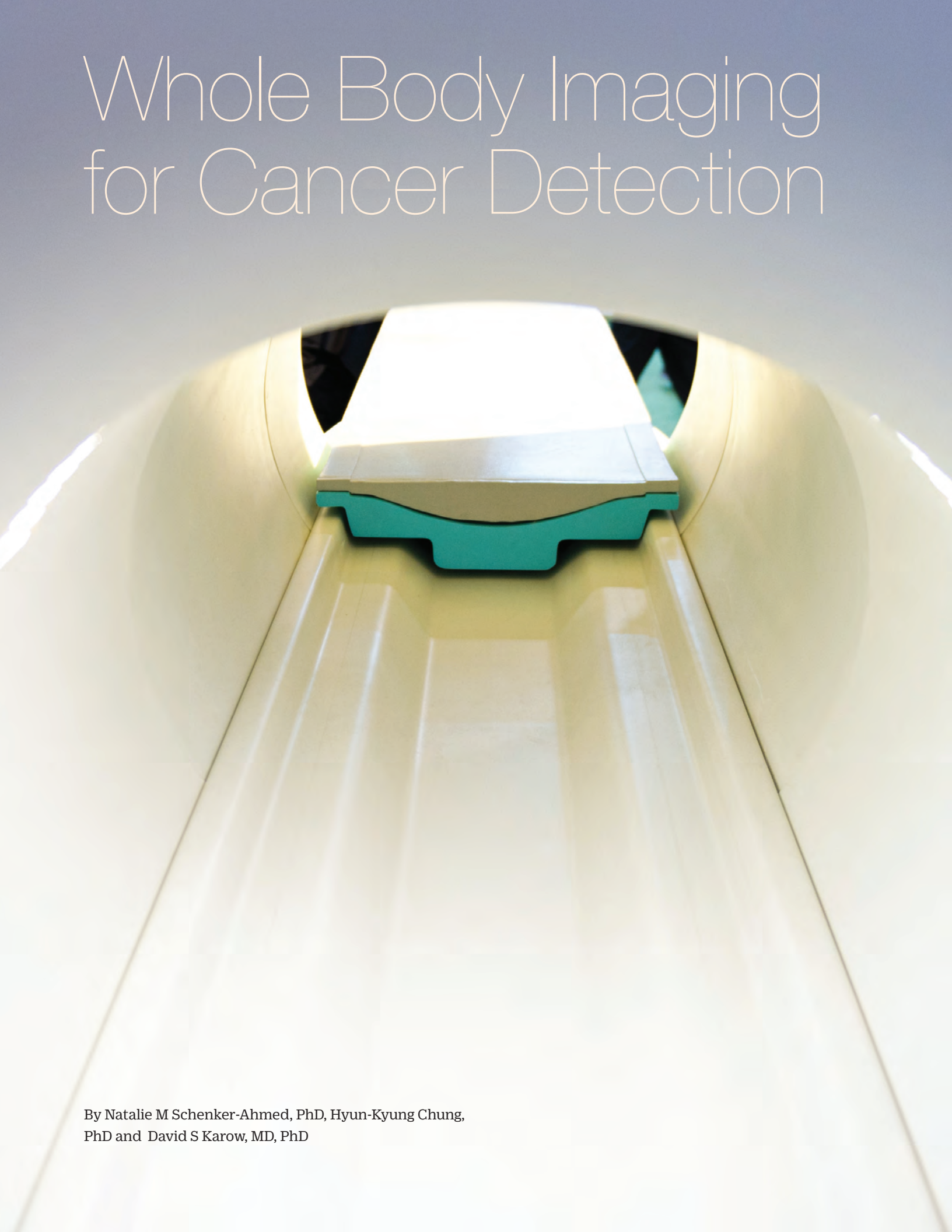
ABOUT THE MASSACHUSETTS GENERAL HOSPITAL
Massachusetts General Hospital, founded in 1811, is the original and largest teaching hospital of Harvard Medical School. The Mass General Research Institute conducts the largest hospital-based research program in the nation, with annual research operations of more than $1 billion and comprises more than 9,500 researchers working across more than 30 institutes, centers and departments. In August 2020, was once again named to the Honor Roll in the U.S. News & World Report list of "America's Best Hospitals."

We're also looking at proteins in the blood that provide a kind of fingerprint or evidence that can tell us where a tumor is located and whether it's malignant or benign.

There is no place on earth like it, and it is a lens on the future... not only for our health but for the future of the industry. It functions on the bleeding edge of preventative medicine. It's the opposite of what our health care system is today...

JEFFERY BROWN
100+ BY HEALTH NUCLEUS MEMBER

Whole Body Imaging for Cancer Detection



By Natalie M Schenker-Ahmed, PhD, Hyun-Kyung Chung, PhD and David S Karow, MD, PhD

Whole Body Imaging is used to create a representation of the entire body in a single procedure. Both computed tomography (CT) and magnetic resonance imaging (MRI) may be used, but generally for different purposes. Because of the significant radiation exposure from a CT scan, it is not generally recommended for screening in healthy individuals. CT is a form of X-ray and uses ionizing radiation that can damage DNA and may increase a person's long-term risk of cancer. Positron emission tomography (PET), which is combined with CT to look for metastasized tumors exposes the patient to even more radiation through an injection. For the purpose of cancer screening, particularly in individuals who are at high risk for developing cancer, MRI is the recommended technology.[1-3] Furthermore, studies have well-documented the ability of WB-MRI to detect cancer[4-7], to monitor disease progression, and to assess therapy effectiveness[8-9]. Thousands of WB-MRI examinations have been performed all over the world for members of health check-up programs, including thousands of patients at our own Human Longevity. Its high sensitivity for detecting early stage cancers, makes whole-body MRI an essential element of proactive health care management. Moreover, for individuals with some cancer predisposition syndromes, a lifetime risk of developing cancer has been estimated to be between 73% and 100%[10] and early detection is particularly critical. A cancer discovered at an early stage can often be treated on an outpatient basis with significantly lowered costs and quality of life impact relative to treatments for late-stage cancer. Furthermore, targeted interventions can appropriately manage the disease to allow longer, healthier life.

Studies using non-invasive MRI to detect cancer

One type of magnetic resonance imaging, known as diffusion-weighted imaging (DWI), has been used for detecting the presence of tumors for nearly 20 years. This type of imaging measures the way that water moves in the body, and tumors have a characteristic signature that differentiates them from surrounding tissue. As a result, the DWI signal "lights up" when there is a tumor. Numerous studies have shown this type of MRI to be very useful for identifying tumors in the brain[11-12], prostate[12-13], and breast[14-15] among others. In addition, morphologic correlations with multiple anatomic images improve the accuracy. MRI is capable of characterizing tissues in many different ways to differentiate abnormal pathology and

normal tissue.

Whole Body Imaging at Human Longevity

The imaging protocol at Human Longevity provides a comprehensive cancer screening of many core organs, including dedicated imaging of the brain, liver, pancreas, prostate (for men), and pelvis (for women). Whole body MRI scans include a fully automated visualization tool for cancer detection. Color-coded "heat" maps overlaid on whole-body anatomic MR images enhance the ability of reading radiologists to detect pathological features (such as cancer) quickly and accurately without the use of injected contrast agents and ionizing radiation. The Human Longevityradiology team has unique and unparalleled expertise in whole-body interpretation, having read close to 5000 whole-body imaging exams.

Unlike other types of full-body scans sometimes used for whole-body screening, radiation-free MRIs allow for yearly repeat analysis, without increased risk of DNA damage and subsequent cancer. The 3D imaging examination of the body anatomy and function can detect unsuspected disease in the earliest stage. Furthermore, ongoing annual assessment enables the construction a comprehensive precision baseline for every individual patient. If, in the future, abnormal findings arise, this baseline enables diagnosis and treatment greater precision and accuracy. Also, yearly assessment provides each patient with updated reports that track meaningful imaging biomarkers for monitoring and optimizing the their health over time.

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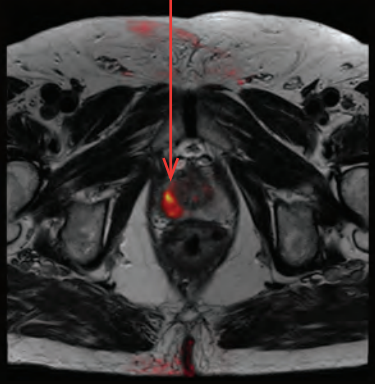
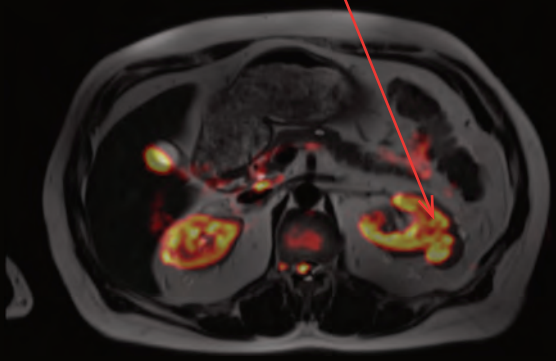
Prostate Cancer



Renal Cell Carcinoma



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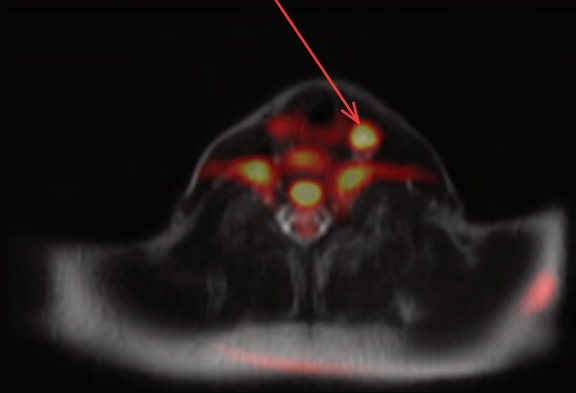
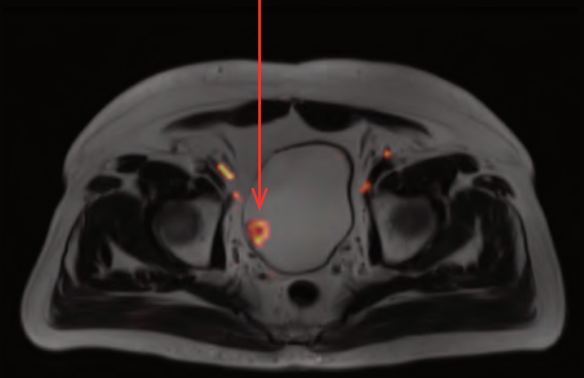
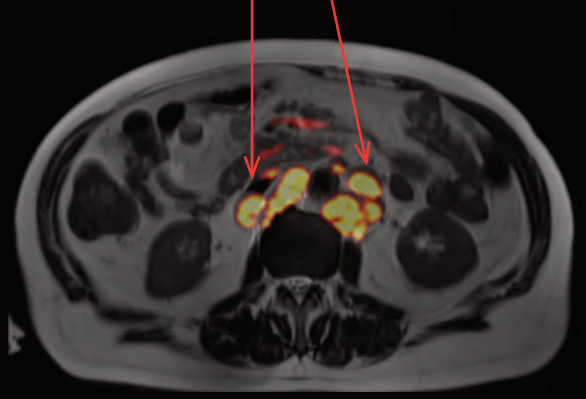


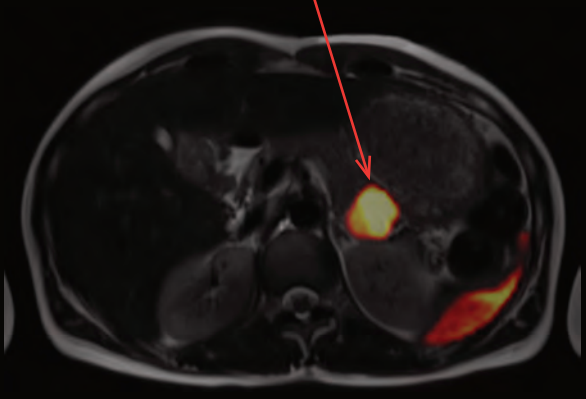
Bladder Cancer



Follicular Lymphoma



Pancreatic Cancer



The Importance of Whole-Body MRI for Cancer Detection: An Interview with Dr. David S. Karow, MD, PHD

President, Chief Innovation Officer and Chief of Radiology, Human Longevity, Inc.
Associate Professor of Radiology, University of California, San Diego

Dr. Karow's mission at Human Longevity is to help catalyze the world's transition to 100+ living. An innovative leader in MR Imaging and genomic analytics, he reminds clients interested in the Human Longevity 100 + platform that they can take actionable steps to improve their health and live not only longer, but healthier longer. Dr. Karow graduated from medical school at the University of Michigan, Ann Arbor in 2005 in a combined MD/PhD program with a distinction in research and completed residency and fellowship at UC San Diego and UC Los Angeles, respectively. He is co-author or primary author on numerous publications focused on early detection of chronic age-related disease using imaging and genomic biomarkers including prostate cancer and Alzheimer's Disease

Why you are so passionate about the use of whole-body MRI for cancer detection?

During my fellowship at UCLA in diagnostic body imaging and nonvascular Interventional Radiology, I was struck by how many of the tumors we were treating were found serendipitously with imaging. It became clear that we needed some kind of organized, strategic methodology—a systematic approach for identifying cancer. Our approach has been to develop a multimodal systematic paradigm for detecting tumors integrating data from imaging, genetics, and blood biomarkers.

What is the role of whole-body MRI in early cancer detection?

Whole-body MRI is one of the three primary tools in our toolbox for detecting cancer, along with germline genetics through whole genome sequencing, and liquid biopsy. However, there is no silver bullet approach, and imaging needs to be performed in concert with the other tests, because, as with any test, there may be false positives and false negatives. When we use whole-body MRI together with all of these other tests, then we give our clients the best opportunity to identify early-stage, high-grade cancer and minimize false positives and false negatives.

Can you provide a specific example of a situation in which the multi-modal approach would be particularly helpful?

One example would be finding an indeterminate lesion in the prostate in a male client. Because it is indeterminate, we can't say definitively that it's prostate cancer or benign. In that situation, we can use other data, including a patient's family history and their clinical metadata, in addition their germline genetics and blood data to assess his prostate cancer risk. If the other data suggests his risk of prostate cancer is high, then we are more likely to recommend follow-up like getting a biopsy. In reverse, if there are no other risk factors: no clinical family history and no risk indicated via liquid biopsy or germline genetics, we are more likely to recommend watching the lesion and re-imaging in six months. If there are no changes at that time, we can say it is likely benign.

What types of tumors can be detected using whole-body MRI?

We have reliably detected a wide variety of high-grade early-stage solid organ tumors including kidney cancer, tumors of the kidney collecting system, bladder cancer, prostate cancer, ovarian tumors, colon cancer, brain tumors, head and neck tumors, lung cancer, mediastinal lymphoma, follicular lymphoma, pancreas, adrenal, and thyroid.

What would you say to a client who is worried about the risks of annual MRI screening?

Whole-body MRI has no radiation and no IV contrast, so there is no risk directly from the procedure itself. However, like any procedure or test there is a risk of false positives, meaning that we may find something on the imaging that turns out to be actually benign or of no clinical concern. A false positive finding can mean that a patient undergoes downstream testing or even invasive procedures like a biopsy that he or she would not have had to go through otherwise.

We take the potential of false positive findings seriously, and act to minimize that potential in two primary ways. One is the multi-modal approach. We have multiple types of testing which can give us further evidence in support of or mitigate against an indeterminate finding. The second way is the longitudinal approach. Every year we conduct an array of data-driven precision medicine-based tests for every client. The resulting longitudinal data set provides greater certainty regarding findings. We know whether a finding has been there for a long time or if it just appeared. A finding that appears unchanged year after year is not concerning, but one that suddenly appears or has changed significantly gives us greater confidence to recommend follow-up testing and treatment.

How many false positives are you aware of in the history of Human Longevity testing?

Out of almost 6,000 clients that we've seen to date, I can only think of three false positives, and two may or may not actually be false. One client who had a very large soft tissue lesion in the mediastinum, which is the center of the chest, that turned out to be simply a very unusually large benign lymph node. That person did have a biopsy that turned out to be negative, and there were no complications. The other two instances were suspected prostate cancer where the biopsy results came back negative. For now, they qualify as false positives, but it also possible that the biopsies missed the cancerous part of the prostate. When those clients return, we will continue to follow their imaging to make sure that the suspected tumors have not changed.

What other limitations are there currently for cancer detection with whole-body MRI?

Whole-body MRI is not perfect, and we can't detect all types of solid organ tumors. Because of how we currently acquire the imaging, there are three types of tumors that we cannot reliably detect: 1) skin cancer, 2) tumors of the gastrointestinal tract, and 3) breast cancer.

1) We simply don't really look at the skin with MRI. 2) Detection of gastrotintestinal tract tumors is limited because we do not currently ask clients to clear their GI system of contents. However, in spite of that we have identified at least one case of colon cancer using whole-body MRI, so it is still possible. 3) All data indicates that accurate detection of breast cancer using MRI requires administering IV contrast, which we do not currently do as part of the annual screening. However, we will soon be adding breast imaging with IV contrast for as an option for women who are candidates.

What do you see as the future of MRI technology and cancer detection?

I think we will get better at identifying smaller tumors that are high grade as the imaging technology advances. There are three main technical limitations for MRI imaging: spatial resolution, meaning our ability to identify smaller tumors; contrast to noise, in other words, how much signal are we able to separate from background noise; and the third would be time. I could probably identify most really small tumors if I asked you to stay in the scanner for 24 hours, but that's not possible. So as the field advances, we are going to be able to identify smaller tumors, higher grade tumors with better contrast to noise and at faster scan times than we've ever been able to do before.

I expect that the technology will improve such that breast cancer will be detectable reliably without IV contrast. Currently, annual screenings are performed using mammograms, which use a small amount of radiation and are quite uncomfortable. With improved MRI technology, we are hopeful that women would be able to have their breast cancer screening completely without radiation or administration of contrast. We expect that an annual non-contrast MRI could complement or even potentially replace mammography as the first line screening in our female clients.

As MRI technology improves, we also look forward to a time when everyone can have a fast (less than 30 minutes) non-contrast whole-body MRI as part of their routine preventive care. With this MRI we will be able to identify ninety plus percent of all early-stage high-grade solid organ tumors, including breast and prostate and GI and pancreas, kidney and collecting system and head and neck and brain et cetera, all without any radiation or risks from IV contrast.

Do you see artificial learning (AI) as something that will help MRI technology?

I think artificial intelligence and machine learning can help MR imaging in a number of ways. One is in pulse sequence optimization. Pulse sequences are the individual MRI sequences that we use across the body to identify cancer. In the next five years, we will see advancements using artificial intelligence to optimize those sequences to enhance the ability to find the cancer at a faster scan time. In another way, AI and machine learning may be critical to the democratization and demonetization of whole-body imaging. With AI and machine learning we could, significantly increase the efficiency and accuracy of the radiologists so that they can confidently read and report on 3-4 times as many whole-body MRIs per hour. Currently, whole-body MRI is quite expensive when you compile the costs of the MRI scanner, all of the software, the radiologist, and the interpretation time. With AI and machine learning, costs could come down and access would greatly improve.

Why should someone choose the Human Longevity to have their annual MRI screening?

Human Longevity has been uniquely positioned in this space for over four years. To achieve the leadership position we have in early cancer detection requires the proper hardware, the proper post-processing software, as well as advanced imaging techniques that are only obtainable via close working relationships with vendors. Furthermore, it requires radiologists who are not only sufficiently trained, but also have experience in reading these types of images.

Beyond that, as I mentioned earlier, the strength of whole-body MRI is greatest when performed in conjunction with the whole precision medicine data-driven suite of testing. We don't do each component a la carte, they are all part of a comprehensive multimodal data-driven approach.

In addition to using whole-body MRI as a screening tool, an equally important component of our whole-body imaging is the derivation and collection of personalized quantitative imaging biomarkers. These biomarkers can help to predict future risk for chronic age-related disease including measures such as visceral adipose tissue, which is a risk factor for many cancers.

Lastly, we are an outcomes-based care delivery company. I don't think there is any other health services company on the planet that credibly has as its mission and vision to help you to live to 100 plus healthily. We back up that mission with a serious data-driven multimodal approach that ensures our healthcare delivery is outcomes driven. What is the outcome? It is 100-plus, and we believe that we have the data and the clinical team and the know-how to actually drive meaningful decision support to get to you to that 100-plus.

Joe Nevin, Founder of Ski For Life™ and bumpsforboomers.com

Health is the New Wealth: A Patient's Perspective

Q&A with Joe Nevin, a multi-year 100+ patient who shares his very personal experience, and perspective, on the value of membership.

What originally brought you to 100+?

My story with Human Longevity begins 60 years ago with my then high school classmate, now Dr. J. Craig Venter. While our paths separated after High School, we reconnected after Craig had sequenced the first human genome and co-founded Human Longevity, Inc. and the Human Longevity. This new company intrigued me, and I asked Craig a million questions. Ultimately, he suggested that if I were to go through the Human Longevity process, all my questions would be answered. So, in September of 2017 my wife and I flew to La Jolla, CA for our first 100+ experience.

Can you describe the experience of visiting the first time?

Visiting 100+ for the first time was very exciting and I was eager to better understand this new medical concept. The staff was very professional, and the state-of-the art facility offered a unique blend of a relaxing spa combined with a cutting-edge medical facility. I received a detailed schedule for each component of 100+. My personal suite with a couch, bathroom and assortment of healthy snacks was my "home base" between the different tests.

The experience was akin to being a pioneer of personalized medicine. My whole genome would be sequenced. A state-of-the-art 3 Tesla MRI would be producing high-resolution images of both my brain and the major organs in my body - without radiation. The results of those tests would be integrated into a personalized early warning system to proactively identify any medical problems that might exist, even before symptoms appear. I was eager to participate in this transformational approach to health.

Did you find your 100+ Results valuable?

Yes, without a doubt. Going into my 100+ experience, I considered myself healthy. After all, I live at 8,000 ft. elevation in the Rocky Mountains, I founded a mogul skiing program in Aspen and ski 100+ days per year. My wife and I hike, bike and fly fish during the summer.

My results were not at all what I expected but I consider myself one lucky guy. Here are 3 examples of how my 100+ results have been incredibly valuable: *(I am waiving all my HIPAA rights because I hope this is a story that everyone can benefit from):*

The most significant result was that the MRI discovered a 2.8cm tumor on my left kidney (renal cell carcinoma). Finding this cancer early was a life-saving discovery for me. 100+ connected me with Dr. Steven Raman, a world-class interventional radiologist and expert in tumor ablation, at the UCLA Medical Center. Because the cancer was caught early, I was able to have the tumor removed without traditional surgery in a same-day, outpatient ablation procedure without the need for chemo and radiation. During this experience I learned that kidney cancer has no symptoms until it metastasizes, and kidney tumors tend to metastasize around 5cm. I can't thank the Human Longevity medical team enough for catching my kidney cancer early when it could be easily treated.

I also discovered that I had an elevated liver fat of 10.8%, an early warning sign I was on a trajectory to develop type 2 diabetes. At no time in my long history of annual physicals had anyone ever measured, or even mentioned,

the topic of liver fat. 100+challenged me to reduce my liver fat to 4% or less and I exceeded that goal by following their recommendation to reduce processed carbohydrates, increase cardio exercise and move to a more plant-based diet. A side benefit - I also lost about 20 pounds. This is another example of how a health risk can be identified and resolved early before a major health problem develops.

A third finding I want to mention is related to "peace of mind". Both my mother and her sister died from Alzheimer's. For a long time, I had been concerned that I might have a genetic pre-disposition to contracting this disease. My genetic analysis did not identify any high-risk genetic variants for dementia. There are also two predictors of Alzheimer's that can be detected via MRI imaging: atrophy of your hippocampus and increasing amounts of white matter lesions in the brain. I received positive news about both. The volume of my hippocampus is statistically larger than 76 percent of the people who are my age and gender. And, my brain has no detectable amount of white matter lesions. All of these results eased my concerns. Importantly, metrics like these are just not available in a typical annual physical exam.

Joe and his wife Nancy with their Bernese Mountain Dog Gracie

What were your thoughts after receiving your 100+ findings?

Five months before my first Human Longevity visit, I received my normal annual physical. At the end of that exam I was given the all-clear sign and that I was "good to go" for another year. So, after I received my 100+ results, I began ask, "What's wrong with this picture?"

Thinking through that question I had an aha! moment. I realized that the US health care system is upside down. It is reactive rather than proactive. You are healthy until you are not. The health care ecosystem is primarily designed to respond to symptoms. Treatment starts after a symptom appears. But, sometimes that can be too late: the disease requires serious treatment or has progressed beyond treatment. Or, tragically, an individual suddenly dies from an undiagnosed underlying medical problem. I've personally experienced more friends than I can count on one hand who unexpectedly died too young from a heart attack, stroke or discovery of late stage cancer.

What brings you back to 100+ for return visits?

Well, if you haven't guessed it already, I've become a rabid believer in the value of proactive medical care. As of 2021 I have completed four consecutive annual 100+ assessments. Each year I receive personalized metrics that enable me to answer the question: "How do I REALLY know that I am healthy?

What would you say to people who don't understand how they could benefit from visiting 100+?

I would say that 100+ offers the best logical, practical and systematic strategy available today to proactively manage your health and increase your odds of living a long, healthy and active life. And, don't confuse looking like you are in good shape with being healthy. Just because you look healthy from the outside doesn't mean that you are healthy on the inside

Anything else you would like to mention?

When people have a conversation about health care, I've noticed that the discussion either becomes political or turns to the rising cost of health care. We have been trained to think about health care as an expense, rather than an investment. It's interesting, however, that most of us likely have a financial advisor who proactively manages our assets for retirement. If your retirement account was valued at half a million dollars you would typically pay 1% of the value of your portfolio, or $5,000 per year, for someone to proactively manage your assets. Most people don't think twice about that expense. That begs two important questions: Who is proactively managing your health? And, might proactively managing your personal health even be more important than managing your finances? I've made my choice, but I'll leave everyone with those two questions to ponder.

"When people have a conversation about health care, I've noticed that the discussion either becomes political or turns to the rising cost of health care. We have been trained to think about health care as an expense, rather than an investment."

Joe Nevin

Joe skiing mogul and powder terrain in Aspen, CO

CASE STUDY: LUNG CANCER

An exceptionally bright and athletic 54-year old female presents to 100+ with her husband. She works in finance and heard about 100+ through a speech by J. Craig Venter. She denies any serious medical issues and is primarily interested in the full body MRI and genetic sequencing because she has a family history of breast cancer.

She knows she has borderline elevated cholesterol from lab work over the years, but she has not considered taking medication because she has worked to manage this with a healthy lifestyle.

Personal medical history and lifestyle:

- Diet includes 15 servings vegetables and 5 of fish weekly
- Exercise includes more than 2 days a week vigorous exercise with a personal trainer including weights and cardio
- Alcohol: 1-2 drinks
- Non-smoker
- Routine cancer screenings all negative
- Very healthy, very active, enjoys the outdoors

Relevant family history:

- Mother, sister and maternal grandmother all diagnosed with breast carcinoma. Testing indicated her sister's cancer was BRCA negative.
- Father had Non-Hodgkin lymphoma and a coronary bypass surgery.

Human Longevity Results

Labs:

- Elevated total cholesterol 207 (range 100-199)
- Elevated LDL cholesterol 127 (range <99)
- Vitamin D deficiency 28.7 (range 30-100)

Imaging:

CT:

- 2.4cm spiculated right lower lobe soft tissue density mass lesion, suspicious for malignancy; corroborated on whole body MRI with restricted diffusion
- Agatston calcium score 59, mildly increased risk of coronary artery event (93% percentile for her age, gender and ethnicity)

Whole body MRI:

- Right lower lobe spiculated, nodular lesion with restricted diffusion corresponding to lesion seen on CT
- liver fat 2.1% (range <4%)
- R2* 46.1 (range <80)

Brain MRI:

- Normal with minor white matter hyperintensities

Cardiac Echocardiogram:

- Normal structure, and cardiac function

Genetics:

Medically Significant Findings (rare monogenic variants):

- No disease risk findings

Polygenic Risk Scores:

- Coronary Artery Disease 98%, risk is 1.6 times that of an average person
- Elevated LDL Cholesterol 98%, risk is 1.2 times that of an average person
- Uterine Fibroids 98%, risk 1.6 times that of an average person.
- All others low or average, including all cancer polygenic risk scores

Diagnosis:

1) Suspected lung malignancy;
2) Coronary Artery Disease

Follow-up

Day 1: Patient was seen by her general practitioner the same day as her 100+ visit who immediately scheduled her a visit with a pulmonologist.

Day 2: Patient saw the pulmonologist, who ordered the follow-up PET/CT scan.

Day 4: Patient underwent the PET/CT scan.

Day 7: Patient met her lung surgeon and received results of the CT scan. She was told that based on the imaging, it was most likely malignant. Surgeon recommended a minimally invasive video-assisted thoracoscopic surgery with an 85% chance of being a definitive cure.

Day 23: Patient underwent surgery removing the lower right lobe of her lung including the tumor. Pathology indicated the tumor was malignant but the lymph nodes were clear of disease (indicating no spread of the cancer).

Day 25: Patient was released from the hospital to return home.

Day 26: Patient was able to walk and bike with no need for pain medicine beyond ibuprofen.

Following month: Back to work and able to travel internationally.

Six weeks after: Patient was fully functioning and able to take on one of the highest leadership roles in her company.

How did the 100+ findings affect the standard clinical pathway for this patient?

This patient would never have been screened for lung cancer in the standard clinical pathway. She had no known risk factors (she was never a smoker or exposed to other high-risk substances to her knowledge), and she led an active, healthy lifestyle. Additionally, the standard clinic pathway had failed to mitigate this patient's coronary artery disease. Because of the results from her 100+ assessment, she met with a cardiologist to optimize her cardiac risk factors after she had resolved her cancer diagnosis.

Comments from the patient:

"I'm immensely grateful that 100+ and this cool new technology found my tumor in the first place. My surgeon advised me that if I'd discovered it once I was symptomatic, it might have been stage 3 or 4, metastatic, and we'd have a different conversation about my life expectancy. But I'm hugely thankful to everyone at HN.

"No one would have looked for this. I am otherwise in excellent health in every way. My 'cancer experience' is over and done in 24 days."

Physician's Comments:

I have been informing patients of their cancer diagnoses for over 20 years – it's one of the most unwelcome conversations I have with people. But, when there are no symptoms and no evidence of spread of disease, it's a profoundly different conversation. Based on her history, I expected to be able to give her the clean bill of health she deserved. But, as outlined above, things went a little differently. But my favorite part about that day is that we were able to guide her back towards the path of being well – before she even knew she had a disease.

I couldn't have asked for a better follow up plan, because she already had an appointment with her primary doctor later that day. Knowing that there is a common misconception that doing full body scans will lead to many false positives, I was prepared to explain why her lung mass was concerning to me. I received a call from the patient at her doctor's office later that afternoon. Her doctor and I brainstormed the best way to get next steps expedited. The next step was a pulmonologist and further imaging. The following week, I got a call from a surgeon who had decided to remove the lesion rather than biopsy it – which was not something he had frequently done. But even a biopsy would cause significant trauma to her lung. Also he knew she was young and active and he wanted to limit how much lung tissue would be destroyed. We agreed that the best approach was to remove the mass as soon as possible.

I received a text from the patient the night after her surgery. The mass was gone, and she was okay. She texted that it was cancer, but all the lymph nodes were normal (meaning there was no evidence of spread).

We all have parts of our story that go in ways we didn't expect. I'm honored to have been able to alter a small part of hers.

Robyn Heister, MD

Implications:

The patient's tumor was discovered at stage 1. If her cancer had been discovered at stage 3 or 4, her relative chance of survival 5 years later would have been 4% (SEER data).

DNA, Genetic Variants and Cancer Risk

The human genome is the complete set of genetic material needed to create and maintain an individual. This genetic material is DNA or deoxyribonucleic acid. It is packaged into 23 pairs of distinct structures called "chromosomes". Half of your chromosomes can be traced back to your mother, and the other half to your father. Both men and women share 22 pairs of chromosomes, labeled from 1 to 22. Additionally, women have two X chromosomes, and men have one X and one Y chromosome. In addition to the 23 pairs of chromosomes, genetic information is also contained in DNA found in the mitochondria, the energy-producing organelles found in each cell of your body. Mitochondrial DNA is inherited exclusively from your mother.

DNA is made of two long strands of 4 building blocks, called "nucleotides" or "bases": adenine (A), cytosine (C), guanine (G), and thymine (T). In order to fit into a cell, DNA forms a characteristic double helix structure in which bases on the two DNA strands align, such that adenine (A) pairs with thymine (T) and guanine (G) pairs with cytosine (C). Because of this pairing, DNA sequence length is given in base pairs or "bp". The human genome has about 3.2 billion base pairs.

The information stored in DNA is used by cells to produce proteins. Proteins are large molecules that produce energy, create tissues, digest food, enable movement, and perform many other critical roles in the body. A string of DNA bases that contains instructions to make one protein is called a "gene". It is estimated that the human genome contains about 20,000-25,000 genes. You have two copies of each gene; one is inherited from your mother and the other is inherited from your father.

To produce a protein, the sequence of DNA bases in a gene has to be translated from DNA building blocks (A, C, G, T) to protein building blocks called "amino acids" (you may remember some amino acids by name, for example, proline, arginine, methionine, and others). DNA is first copied to a type of molecule called messenger ribonucleic acid (mRNA) in a process called transcription. mRNA is then translated into a protein when the nucleotides A, C, G, and U (U replaces T in mRNA) are used to build a set of amino acids into a protein.

What happens when one DNA base is replaced with a different DNA base, for example, sequence ATGAAC becomes ATGACC? This difference is called a "genetic variant". In most cases, such changes in DNA do not result in changes in the produced proteins. In some cases, however, genetic variants can lead to proteins with altered functions, or cause a change in how much protein is made. When a change in the protein happens, it is not always harmful, but can be favorable or neutral. Unfortunately, some changes in DNA are harmful and lead to proteins that cannot perform their function due to errors in their structure or insufficient amount. When a certain protein cannot perform its function, a disease can develop. Genetic variants with effects so strong that only one error is sufficient to cause a disease are rare, and we call those "monogenic variants". However, harmful variants with small or medium effects are more frequent. They are not capable to cause the disease by themselves but having several of them in different genes can predispose you to develop disease and these together can be used to generate "polygenic risk scores".

To learn which genetic variants an individual has, the

DNA is sequenced which allows the order of the bases A, C, G, and T present in all chromosomes to be read. Then, that DNA sequence is compared to the sequence that represents the DNA of an average healthy human. Any differences, or genetic variants, are noted and analyzed. Over four million variants in approximately 22,000 genes are evaluated. Of those 22,000 genes, 3,533 are known to be associated with disease. Further, in-depth genomic analysis is performed on 210 genes that are known to be associated with increased risk of developing cancer, heart and vascular, metabolic, and neurodegenerative disease. And finally, genetic variants are analyzed by a set of statistical models providing important clues into an individual's disease risk.

High-risk genetic variants that result in strong effects on protein function are rare and the diseases they caused are called "rare diseases", "Mendelian diseases", or "monogenic diseases". "Mono" indicates that disruption of function of a single gene is sufficient to cause the disease.

A different type of genetic variants, low-risk variants, contribute to the development of common diseases including cancers. Each such variant has only small impact on the protein function or a body's process like inflammation and does not cause the disease by itself. These variants with small effects are common among people, being found in at least 1 in 20 individuals, but sometimes as common as 1 in 5 or more (in contrast with high-risk variants that are found in less than 1 in 100 individuals). Only when several low-risk variants are found together in one individual can they have a strong enough impact to be associated with an increased genetic risk for a common disorder.

In reality, many diseases have both monogenic and polygenic subtypes. For example, variants in the BCRA1 and BRCA2 genes are considered disease-causing as lifetime risk of developing breast cancer for women having such variants is high (the risk reaches 38% to 87% and significantly exceeds the risk of breast cancer in general population estimated as 12%[1]). Thus, BRCA1- and BRCA2-associated hereditary breast and ovarian cancer is considered to be a monogenic condition. However, only 5 - 10% of breast cancer patients have BRCA1 or BRCA2 variants or variants in other high-risk genes[2,3], leaving a significant number of breast cancer cases that are cases with significant contribution from genetic factors but with a principal role of environment and lifestyle.

While high-risk variants can impart risk independently, the risk conveyed by low-risk variants has to be evaluated as a group. To assess risk in this way, an individual's polygenic risk score for a particular disease is calculated by summing the effects from multiple variants present in that individual's genome. That score is compared to the scores of other people. If the individual's score is higher than average, then they have increased risk, whereas if the score is lower, they have decreased risk relative to the general population.

Having a high polygenic risk is not the same as having a variant causing a rare disease, but it means that your genetic predisposition is increased. Environment and lifestyle are also important contributors to disease risk, so if you have a high polygenic score, you should feel especially motivated to maintain a healthy lifestyle. Minimizing other risks will allow avoiding several risk factors, genetic and lifestyle-related, affecting your health at the same time.

Using polygenic scores for disease risk prediction is a relatively new approach in clinical practice[1-4], and as with any new technologies, there are limitations. One, most polygenic risk models created so far have used primarily data from people with European ancestry. This means they may be less accurate for people of other backgrounds. Two, polygenic risk scores are still rather limited in predicting who will actually develop a disease; incorporating new variants as they are discovered will likely improve risk scores in the future.

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Radical Science
Radical Service
Radical Results
Be 100+
100+ Ongoing 365 Health Assessment
The most comprehensive data-driven health exam that includes whole genome sequencing and update, whole body, brain and cardiac imaging, coronary calcium scoring, body composition, advanced blood biomarker analysis and wearables all of which can lead to pre-symptomatic diagnosis of cancer, cardiac disease, neurodegenerative and metabolic disease.
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The Role of Genomics in Detecting and Preventing Cancer: An Interview with Dr. C Thomas Caskey, MD, FACP, FACMG, FRSC

Dr. Tom Caskey is an internal medicine doctor with a long research career in genetics and biomedical research. His 50+ years of research have focused on the genetic basis of human diseases. Among his contributions are helping to develop PCR technology for clinical and forensic applications and discovering of the universality of the genetic code. His genetic research identified the genetic basis of 25 major inheritable diseases. Dr. Caskey's current research focuses on the application of the whole genome sequence and metabolomics of individuals toward the objective of disease risk and its prevention.

Why is genetic testing important for addressing cancer?

First and foremost, all cancer is genetic. Cancer occurs because of mutations in certain genes that result in a cell being able to replicate without constraints. There are two ways in which cancer occurs. One way is that the risk for cancer is inherited, and there are several types of cancer that can run in families. The second mechanism is one by which a new "spontaneous" mutation occurs in the DNA in the cells of an individual. Those new mutations have to be in specific genes, either driver genes that can make a cell replicate rapidly or slow-down genes which become non-functional from the mutation.

How does whole genome sequencing (WGS) differ from whole exome sequencing (WES) or genotyping?

Whole genome sequencing provides a clearer and more comprehensive picture than that provided by the targeted technologies.

Whole exome sequencing (WES) only sequences exons, the parts of genes that code for amino acids, the building blocks of the proteins used by our bodies. Where whole exome sequencing can provide sequence data on just 2-3% of the total DNA, whole genome sequencing produces sequence data for all of the DNA . This means that the mutations occurring outside of the exons that can cause cancer would be missed by WES but could be identified via WGS.

Genotyping also serves a purpose, but it is very focused and quite limited compared to whole genome sequencing. WGS looks at the entire DNA sequence where genotyping only looks at specific areas. Say you've lost your wallet in a football stadium. Genotyping is comparable to taking a flashlight and looking for your wallet in just a couple of spots. Whole genome sequencing turns on all the floodlights, illuminating the entire stadium so that you can search around every seat.

How are genomics used to assess inherited cancer risk?

With inherited risk for cancer, it's important to remember that you don't inherit the cancer itself, you inherit the risk of developing cancer. This was first made clear by Alfred Knudson's studies of retinoblastoma. He won the Nobel Prize for making this discovery. He proposed the "two-hit hypothesis" in which you can inherit a mutation that conveys the inherited risk, but in order to develop cancer, you must also have a mutation arise in a cell during your lifetime, resulting in another error in your DNA within that cell that leads to the growth or start of the cancer. With 100+, we perform whole genome sequencing, which with a single test, allows us to look for any inherited variations in your DNA that impart inherited risk of all of the known types of heritable cancer.

What is very important to understand is that DNA sequencing can only identify a risk gene. This is not a cancer diagnosis in an individual, because that takes the second event. For example, 40% of individuals who have inherited a risk for breast cancer will never get cancer..

Another important thing to understand is the impact beyond the individual. If you have inherited the risk of a certain cancer, but you've never had it, your children have a 50% chance of inheriting that risk also. Therefore, the identification of a gene associated with cancer risk in an individual opens up the opportunity to prevent cancer by early diagnosis in that entire family. Anyone who has an inherited risk has a high chance of developing cancer whether or not their parent did. Therefore, when a cancer risk variant is identified in an individual it is very important for all related family members to be tested to find out which individuals also have substantial cancer risk.

What types of cancer are known to run in families?
The ones that have been in the news a lot include breast cancer, colon cancer, kidney cancer, and prostate cancer. However, there are probably 130 to 140 cancer types for which risk can be inherited.

Are there certain populations that need to be more concerned about inherited cancer risk?
Yes, certain ethnic populations can have a higher risk of predisposition to cancers because those genes are more common in the population. For example, Southeast Asians tend to have a higher risk of liver disease and stomach cancer, while individuals with central European Jewish heritage have a higher risk of breast and ovarian cancer. Moreover, nearby Arabic populations also have a high frequency of breast and ovarian cancer.

What about the second category of cancers which are not known to have an inherited risk component?
These cancers do not require an inherited risk and can occur from single mutation events. In fact, these are currently the majority of cancers seen in clinics. New mutations create what we call driver genes, where the single mutation can lead to the rapid replication in the cell, resulting in cancer. A classic example is leukemia. All types of leukemia, both childhood and adult, are due to new mutations arising in the individual.

Dealing with these cancers requires using a variety of strategies other than genome sequencing. Early detection of cancer is critical to getting cured efficiently, as once cancer has spread to other organs, it is much more difficult to cure. However, if you identify the early lesions of cancer then it can be surgically removed. Whole-body MRI scanning, which is discussed at length elsewhere in this publication, can be used to detect and locate cancerous lesions. In particular, whole-body imaging through 100+ has had a great success in the identification of prostate cancer. Furthermore, biomarkers, typically molecules that can be detected in the serum from a blood sample, may indicate the presence of cancerous cells. One example is CA-125 which is often used as a screening test for ovarian and uterine cancers.

A third method of detection also discussed in this publication is liquid biopsy, one example of which are the tests for detecting colon cancer. While, forty percent of colon cancers can be identified through inherited cancer risk, the remainder are not, but may be detected using liquid biopsy. These tests look for abnormal cells that are shed and therefore can be identified by DNA sequencing as cancer cells. A positive result would lead to a follow-up procedure such as a colonoscopy to confirm the result.

Early detection of cancer requires the integration of hi-tech diagnostics, where the data from every test are evaluated by experts and integrated to form a complete picture of an individual's health status. With 100+, we use this multi-prong approach that integrates genomics data, whole-body MRI, blood biomarkers, and liquid biopsy where appropriate.

CASE STUDY: BREAST CANCER

A 63-year-old female visits 100+ with no major health concerns. Due to the in-depth genetic analysis, she is discovered to have a rare genetic variant that conveys high-risk for developing breast cancer. She was referred to a high-risk genetics cancer clinic, where it was discovered that she already had a high-grade, but very small, breast tumor. It was promptly treated, and she recovered quickly.

Personal medical history and lifestyle:

- Prediabetic since age 48
- Hepatitis B positive

Surgical History:

- None listed

Medicials

- Entrecavir

Lifestyle:

- Diet: No red meat; 10 servings of fish/week; 6 servings of fruit/week; 5 servings of nuts & seeds/week
- Alcohol: minimal 0-1/week
- Tobacco: none
- Sleep: 7-8 hours/night
- Activity level: highly active with more than 2 hours vigorous exercise/week

Relevant Family History:

- Father: N/A
- Mother: Heart attack age 70
- Children: 2 healthy daughters

Human Longevity Results / Normal Range:

- Glucose: 117 mg/dL (range 65-99 mg/dL)
- Hemoglobin A1c: 6.2 (range 4.8-5.6; Prediabetic: 5.7-6.4)
- Vitamin D: 30.9 ng/mL (range 30-100 ng/mL)
- Platelets: 98x103/L (range 150-450x103/L)
- Mercury, Blood: 40 g/L (range 0-14.9 g/L)
- Prolactin: 27.9 g/mL (range 4.8-23.3 ng/mL)

Imaging:

CT

- Agatston calcium score 0, very low risk of coronary artery event

Whole Body MRI:

- Liver fat 2.8% (range <4%)
- R2* 65.3 (range <80)
- AMRA body composition / Normal Range:
    - VAT: 1.87 L (range 1.49-3.51 L)
    - VAT Index: 0.69 L/m2 (range 0.57-1.34 L/m2)
    - ASAT: 4.12 L (range 5.55-9.90 L)
    - Total Thigh Muscle: 7.51 L (range 7.46-8.95 L)

Genetics:

- Medically Significant Findings (rare monogenic variants):

BRCA2 variant

- Autosomal dominant likely pathogenic variant associated with hereditary breast and ovarian cancer syndrome
- 40-57% of women with this variant develop breast cancer by age 70
- 13-23% of women with this variant develop ovarian cancer by age 70

Diagnosis:

1) Prediabetes;
2) Elevated mercury;
3) Osteopenia;
4) Low platelets

Follow-up

As a result of the 100+ screening, the patient was recommended to have additional genetic testing to confirm the relevance of her BRCA2 variant. She was referred to Ambry Genetics for mRNA testing, which found that her variant was likely pathogenic. Given the pathogenicity, the client was recommended to be seen at a high-risk genetics cancer clinic, and was referred to the Massachusetts General Cancer Center's Breast and Ovarian Cancer Genetics Clinic. A small but high-grade breast tumor was discovered. She had a simple mastectomy which was able to completely remove the tumor and has recovered well.

Ambry Genetics testing was also ordered for the client's 2 daughters, one of whom also was found to carry the high-risk BRCA2 variant.

How did the HN findings affect the standard clinical pathway for this client?

Client had previously been tested through 23andme genetic testing which missed the relevant genetic variant. Human Longevity's whole genome sequencing and accompanying analysis discovered a critical genetic variant that not only led the client to discover and treat a tumor in herself but has also allowed for her entire family to be tested, one of whom also has the relevant variant.

Perspective from the care team:

The client has 2 daughters and three siblings. One of her siblings, a sister, has had breast cancer. This sister is not

believed to have been offered genetic testing. It would be recommended for any family member to get testing done so that they can know whether they have increased risk also. One of her daughters, has already been found to also carry the high-risk variant, and will now be able to be vigilant going forward. The daughter was further counseled regarding lifestyle factors that could help to mitigate her future cancer risk. Suggestions included maintaining a diet including sulfur-rich plants to detoxify estrogen and also high in fiber to help with gut bacteria balance. Further, proper management of stress can reduce the likelihood of estrogen dominance and healthy sleep is encouraged to keep the detoxification pathways functioning well.

Moving forward, the same variant that predisposed the client to develop breast cancer also predisposes her to develop ovarian cancer. Now that she is aware of her risk, she can engage in ongoing appropriate screening for early detection.

Furthermore, there are non-genetic risk reduction strategies, including diet and consuming foods that are high in phytochemicals, as well as stress reduction. The client's known prediabetic condition for nearly 15 years may have contributed to the development of her breast cancer, and it is important for her overall health including cancer risk to adjust her blood glucose levels through diet, daily exercise, and possibly considering some form of time restricted fasting.

CASE STUDY: BLADDER CANCER

A 64-year old female member of 100+ by Human Longevity is particularly interested about her cancer risk, as she is worried that she had radiation exposure as a child. Her 100+ screening revealed an early stage treatable bladder tumor and also an important genetic finding that conveys increased risk for breast cancer and colon cancer.

Personal medical history and lifestyle:

- No chronic medical conditions
- Reports that she hasn't seen a doctor in over 10 years
- Last colonoscopy in 2008. Screened for colorectal cancer March 2020
- Last mammogram in 2008
- Non-smoker
- No alcohol consumption
- Moderately active (2 hours of moderate activity per week)

Relevant Family History:

- Father suffered a heart attack at 60
- Mother had colon cancer at 84
- Four siblings with no known health issues
- Two healthy children in their 40s

Human Longevity Results / Normal Range:

- Total Cholesterol: 377 mg/dL (range 100-199 mg/dL)
- LDL Cholesterol: 269 mg/dL (range <99 mg/dL)
- LDL particle number: 3485 (range <1000)
- Small LDL particle number: 1618 (range <=527)
- Triglycerides: 256 mg/dL (range<149 mg/dL)
- Lipid Insulin Resistance Score: 57 (range <=45)
- Cardiac C-reactive Protein: 3.85 mg/L (range 1-3 mg/L)
- Hemoglobin A1c: 6.0 (range 4.8-5.6; Prediabetic: 5.7-6.4)
- Vitamin D: 25.6 ng/mL (range 30-100 ng/mL)

Imaging:

CT

- Agatston calcium score 0

Whole Body MRI:

- 2 cm spiculated bladder mass arising from the left posterior bladder wall near the left ureterovesicular junction projects into the bladder lumen. Mass is highly concerning for malignancy and recommend cystoscopy and urology consultation to further evaluate.
- Liver fat 7.5% (range <4%)
- Severely elevated visceral fat VAT Index 1.89 L/m2: range 0.57-1.35 L/m2 (over 90th percentile for sex and age)
- R2* 66.8 (range <80)

Brain MRI:

- Normal

Genetics:

- Medically Significant Findings (rare monogenic variants):

CHEK2 variant

- This gene is associated with an increase risk for breast cancer (1 in 5 lifetime risk) and colorectal cancer
- Recommendations exist from the National Comprehensive Cancer Network (NCCN) for management, updated every year

Current recommendations:

- For women – annual mammogram with consideration of breast MRI with contrast starting at age 40
- For everyone – colonoscopy screening every 5 years beginning at 40 years old
- Recommendation for testing family members for this variant as well

Polygenic Risk Scores:

- Elevated LDL cholesterol 95%, risk is 1.2 times that of an average person
- Elevated total cholesterol 90%, risk is 1.1 times that of an average person
- Multiple Sclerosis 94%, risk is 3.4 times that of an average person
- Venous Thromboembolism 94%, risk is 1.8 times that of an average person
- All others low or average, including all cancer polygenic risk scores

Diagnosis:

1) Suspected transitional cell carcinoma of the bladder;
2) Metabolic disease (prediabetes, elevated liver fat, elevated LDL and total cholesterol, elevated visceral fat)

Follow-up

Day 1: Diagnosis based on 100+ whole body MRI screening

Day 3: Consult with primary care doctor who placed an order for a urology referral

Day 17: 2nd opinion with urologist at a tertiary referral center. On the same day, the patient underwent a cystourethoscopy. The procedure found a large papillary mass concerning for bladder cancer. Patient was recommended to undergo transurethral resection of the bladder tumor (TURBT).

Day 25: Patient underwent TURBT. Pathology indicated a non-invasive low-grade papillary urothelial carcinoma with focal high-grade features. A left ureteral stent was placed at the time of resection.
Day 36: Post-operative visit indicated the patient was doing well.

How did the 100+ findings affect the standard clinical pathway for this client?

The patient had no known traditional risk factors for bladder cancer, such as smoking. However, screening using whole-body MRI read by a uniquely qualified Human Longevity radiologist uncovered an early stage bladder mass that had not yet manifested any symptoms. The tumor is unlikely to have been discovered until symptoms appeared in the standard clinical pathway. Most bladder tumors are diagnosed after symptoms appear, and therefore are more likely to be at a more advanced stage. In contrast, early detection enabled the patient's tumor to be removed at an early stage.

Furthermore, the unique genetic analysis provided by the 100+ assessment revealed that the patient had a genetic variant in the CHEK2 gene that may have influenced her development of bladder cancer. However, the same variant also confers risk for breast and colon cancer. Now that she is a 100+ member of Human Longevity, she will be able to get regular screening that is recommended since she has higher risk of developing these cancers. Also, her children and siblings now know that they should be tested for the same variant. If they have the variant, that would affect the age at which they should initiate colon cancer and breast screening.

Finally, the patient's polygenic risk scores for LDL and Total cholesterol were elevated. If the patient is not able to lower those values through lifestyle changes, the genetic findings would emphasize the potential need for pharmacologic intervention.

Perspective from the care team:

The patient's tumor was discovered before it had spread beyond the inner layer of the bladder wall. The 5-year survival rate of people whose tumor is discovered at this stage is 96%. In contrast, a tumor that extends beyond the bladder results in a survival rate of only 36%. The early detection of the patient's tumor undoubtedly improved her prognosis and it's not unreasonable to assume it dramatically improved her quality of life.

The 100+ screening also uncovered signs of insulin resistance, hyperlipidemia and fatty liver disease. Although the patient is not considered to be obese based on BMI, her visceral fat is severely elevated. It's known that diabetes and metabolic disease can increase the risk of colorectal, breast and bladder cancer , so the patient was motivated to undertake lifestyle changes to improve her insulin sensitivity and hyperlipidemia. Such lifestyle changes will likely reduce her risks of multiple threats to her ability to live a long and healthy life.

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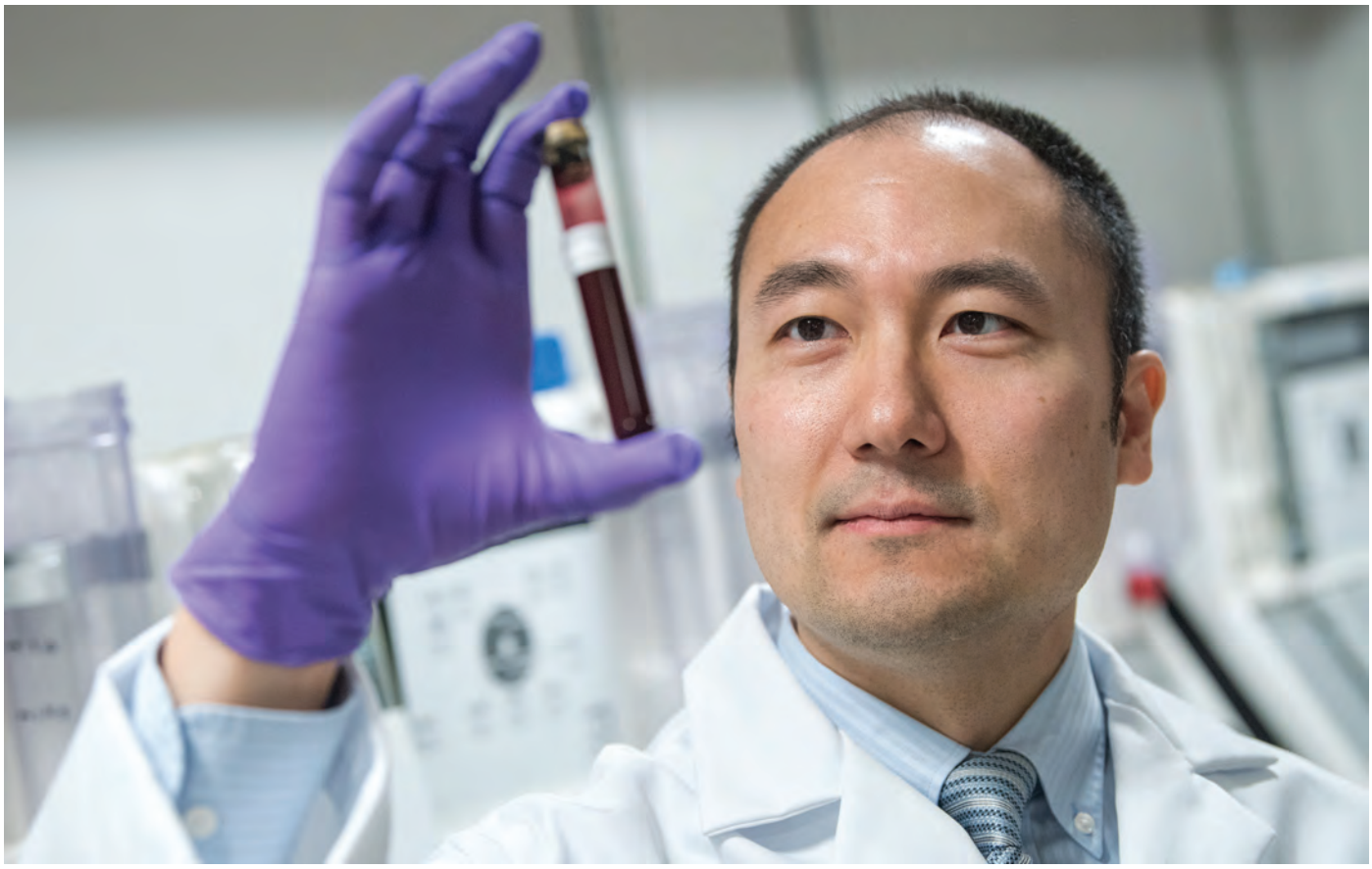


David Miyamoto, MD, PhD, a researcher in the field of early cancer detection, examines a blood sample. Photo by Joshua Touster

Channeling the Future of Early Cancer Detection

In labs across Mass General, researchers are guiding patient blood samples through the tiny channels of an innovative device that could open doors to faster, easier cancer detection.

In his lab at the Massachusetts General Hospital Cancer Center, David Miyamoto, MD, PhD, holds a plastic disc up to the light. It looks like a DVD movie disc but with two tubes attached and a series of tiny channels embedded in it. This device holds great promise for early cancer detection using a technique called liquid biopsy.

"It's really a feat of engineering," Dr. Miyamoto says, standing near a wall of whirring machines known as microfluidic processors as they circulate blood through channels on such discs.

Named the "CTC chip" after the circulating tumor cells (CTCs) which are its quarry, the device removes all normal red and white blood cells from a patient blood sample, leaving only tumor cells and other abnormal blood components behind. The word "chip" is a reference to an early version which resembled a business card-sized microchip.

The CTC chip looks like a DVD movie disc but with two tubes attached and a series of tiny channels embedded in it.
Photo by Joshua Touster

Early Cancer Detection Tools

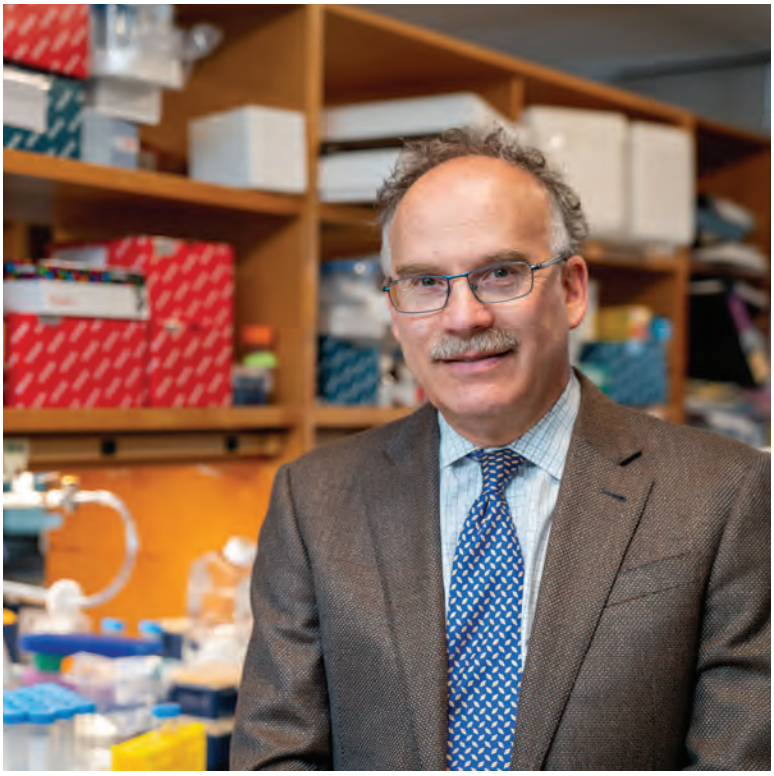
CTCs are hard to find but immensely useful in yielding clues about the presence and characteristics of cancer. The earlier a cancer is found, the more likely it can be successfully treated. Equally important, CTCs can help doctors monitor patients for cancer recurrence.

"It's like finding a needle in a haystack," Dr. Miyamoto says. "We remove the haystack and the needle left behind is the cancer cells."

Dr. Miyamoto is a leader in a collaborative enterprise among physicians, bioengineers and molecular biologists at Mass General Cancer Center and beyond. He and other researchers are advancing cancer detection with liquid biopsy technologies — a new set of tools, including the CTC chip, that analyze blood or urine samples to diagnose cancer.

Liquid biopsy technologies seem poised to change the course of cancer diagnostics in a similar way to earlier cancer breakthroughs, such as the Pap test, which led to a dramatic decline in cervical cancer deaths after it was widely introduced in the 1960s. But while the Pap test screens only for cervical cancer, liquid biopsies can be used for many different types of cancer including liver, lung, prostate and others.

These new technologies hold great promise because they will help us diagnose cancer sooner, with greater accuracy and at a stage when treatments can be most effective



Daniel Haber, MD, PhD, director of the Mass General Cancer Center, is a pioneer in the field of liquid biopsy technology.

Photo by Amanda Kowalski

“A liquid biopsy or test is one of the easiest ways to monitor people. There are so many different options to look at in the blood, urine or even the breath that can tell us about cancer.”

Lecia Sequist, MD, MPH, director of the Center for Innovation in Early Cancer Detection (CIEDC) at Mass General Cancer Center.

"These new technologies hold great promise because they will help us diagnose cancer sooner, with greater accuracy and at a stage when treatments can be most effective," says Daniel Haber, MD, PhD, director of the Mass General Cancer Center.

Dr. Haber is a pioneer in the field. He and Mehmet Toner, PhD, a founding director of Mass General's Institute for Bioengineering and Biotechnology, developed the CTC chip, a first-of-its kind device, in 2008.

Encouraging Collaboration

"There's a lot of excitement here," says Lecia Sequist, MD, MPH, director of the Center for Innovation in Early Cancer Detection (CIEDC) at Mass General Cancer Center. "A liquid biopsy or test is one of the easiest ways to monitor people. There are so many different options to look at in the blood, urine or even the breath that can tell us about cancer."

The CIECD encourages collaboration and partnerships among Mass General Cancer Center patients, researchers, and technology entrepreneurs to drive forward the understanding of early cancer biology, Dr. Sequist says. The center works to support the development of innovative technologies and launch pilot trials leading to early cancer detection and better treatments for patients at Mass General and around the world.

Home of the largest hospital-based research program in the country, Mass General is well positioned to bring together the necessary combination of patients, physician-researchers and bioengineers who can make this work happen, she says, adding that "pairing patients with novel technologies is our hallmark."

Clues to Early Cancer Detection

Liquid biopsies — usually a simple blood test — have several advantages over the traditional tumor biopsy which requires removing a piece of tissue from the suspected tumor, possibly causing pain, infection, other dangerous complications and, sometimes, unnecessary treatments. Using the most advanced molecular and genetic science combined with bioengineering, this multipronged effort is expanding on several fronts.

Researchers are hunting for different substances in the blood, urine or breath that provide clues to cancer known as molecular signatures, or biomarkers. They are using liquid biopsies to investigate substances including circulating tumor cells, DNA fragments (ctDNA), exosomes (packets of molecules given off by tumors) and proteins. These tests reap measurable information that can help identify cancer, guide treatment or, as some researchers hope, prevent cancer from occurring at all.

The CTC chip is one of the most promising advances in liquid biopsy technology. By circulating a patient's blood through its tiny channels using a process developed in the field of microfluidics, the chip finds tumor cells and other substances that reveal information about cancer.

Researchers in several labs at Mass General have already demonstrated the CTC chip's capacity to identify various forms of cancer and the pathologies that lead to them in small pilot studies. They have also developed the ability to monitor patients for cancer recurrence. But large-scale human trials involving hundreds of patients are needed before CTC chip analysis can be used to benefit patients. Philanthropic contributions are needed to move this research to the next level.

Photo by Joshua Touster

A bank of CTC-chip machines whirs constantly as the new technology sifts through millions of blood cells to find the crucial few that indicate the presence of cancer.

Diagnosis and Uncertainty

Dr. Miyamoto was a college sophomore when he learned the importance of early cancer detection. As a student at Harvard University, he watched with disbelief as his apparently healthy roommate fell ill and eventually died from bone cancer. He wondered whether earlier detection would have saved his friend's life.

"That had a huge impact on me," says Dr. Miyamoto, who, 20 years later, is a radiation oncologist leading a research lab.

Dr. Miyamoto works on prostate cancer, which is notoriously difficult to assess. A diagnosis of prostate cancer leaves many men in a state of uncertainty. Most prostate cancers grow so slowly that they pose little danger and require no treatment. But it's hard to know which cancers are likely to grow. The standard test — for prostate specific antigen (PSA) — is often inaccurate or unspecific. As a result, many men undergo monitoring, including repeat prostate biopsies with accompanying pain and side effects.

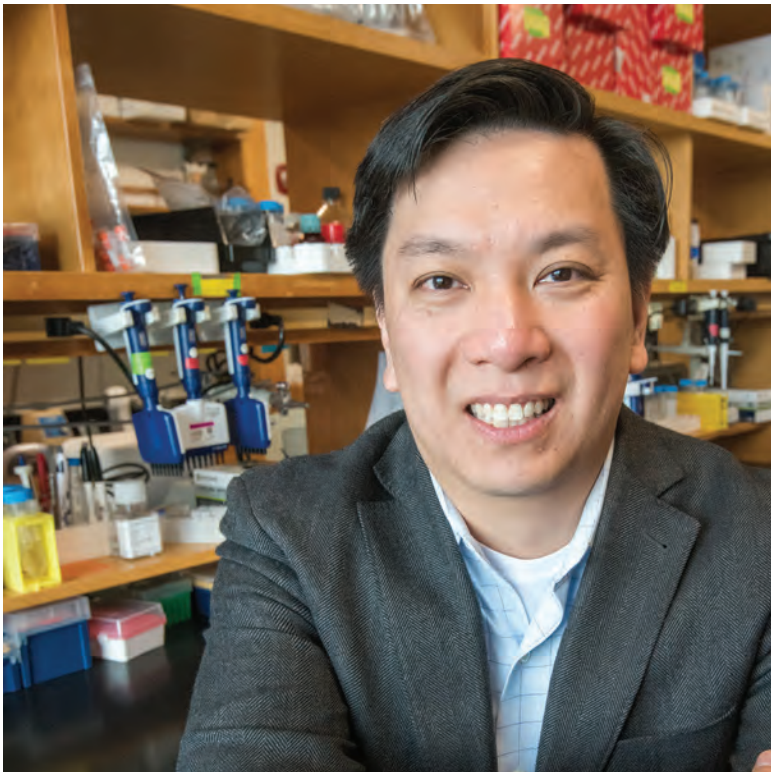
Safer, Easier, Better

Dr. Miyamoto recalls a patient who developed a dangerous infection resulting from the prostate biopsy. No cancer was found. But the man had to be hospitalized for the systemic infection.

He is now working to develop a less invasive test to detect prostate cancer early and help guide treatment. "It would be great if we had a simple blood test that could tell us if a man has prostate cancer and if it is becoming more aggressive and needs treatment," Dr. Miyamoto says.

His pilot studies have shown, among other things, that the cells gathered with the CTC chip can be analyzed to understand a patient's prostate cancer and guide treatment, both for cancers that have spread and those that have not. Larger studies confirming these results are needed.

“My pie in the sky is not just early detection,” he says. “It’s prevention.”



David Ting, MD, seeks to detect early cancer but also to find clues before the disease develops in hopes of preventing it.

Photo by Joshua Touster

Unexpected Discoveries

David Ting, MD, studies liver and pancreatic cancers at Mass General Cancer Center. An MIT engineering graduate turned oncologist, Dr. Ting wants to do what cardiologists have done for heart disease — develop preventive treatments like the widely used cholesterol-lowering drugs that keep arteries clear and prevent serious cardiac conditions.

The surprises he is finding with the CTC chip make him optimistic.

“We were looking for tumor cells,” he says, “but we’re finding all these other cells we didn’t know would be there.” That’s big news, he says, because the damaged liver cells they are finding reveal conditions such as fatty liver disease and cirrhosis — precursors to cancer. Liver cancer, a common cause of death in Asia, is a growing concern in the United States where conditions such as obesity are contributing to its increase.

Prevention as a Goal

Using the CTC chip in small studies, he and colleagues have developed a test that can help determine whether a person has liver cancer or is likely to develop it. They can see the difference between a patient with chronic liver disease and one who already has cancer.

If larger studies confirm that the CTC chip can find biomarkers in the blood that show a patient is heading toward cancer, he says, drugs could be developed to reverse that process.

No single technology will provide all the answers, but with more and larger studies, Dr. Ting says liquid biopsies should open the door to exciting new options.

“My pie in the sky is not just early detection,” he says. “It’s prevention.”

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Physician scientists in Mass General's Avon Comprehensive Breast Evaluation Center are using artificial Intelligence models to predict breast cancer up to five years in advance.
Photo by Shutterstock

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Breast Cancer: Improving Detection with A.I.

With the help of artificial intelligence, Mass General doctors can now predict breast cancer earlier and eliminate racial biases seen in traditional detection models.

Connie Lehman, MD, PhD

Mass General's Constance ("Connie") Lehman, MD, PhD, is chief of Breast Imaging, Professor of Radiology at Harvard Medical School, and co-director of the Avon Comprehensive Breast Evaluation Center. Below, she describes her collaboration with colleagues from MIT's Computer Science and Artificial Intelligence Laboratory and their pioneering work developing an image-based model that predicts breast cancer up to five years in advance.

Why is it important to have better breast cancer risk assessment tools?

Most women diagnosed with breast cancer have no "known" risk factors other than being female. Without accurate risk assessment tools, we over screen many women and under screen others. We knew if we could develop better methods to assess a woman's personal risk of breast cancer, we could redesign our screening programs, tailored to each individual woman's risk.

Using techniques in artificial intelligence (AI), we created a model utilizing data from mammograms and cancer outcomes of more than 80,000 Mass General patients. Our AI model learned subtle patterns in breast tissue that are precursors to breast cancer. These are patterns the human eye cannot recognize, so this approach goes far beyond simply analyzing a woman's breast density on a mammogram.

Each woman's mammogram is then assessed to determine her individual risk at the time of the mammogram, and her risk of developing cancer five years into the future. Ultimately, women will make more informed decisions about their options for screening and risk reduction, and we can provide more effective, less costly care.

What outcomes have you seen so far?

Our models consistently and significantly out-perform available traditional risk models for all our patients. This performance improvement is most dramatic for women of color. Specifically, our research revealed a dramatic racial bias inherent to existing commercial risk models. Those models were almost exclusively developed on European Caucasian populations.

At Mass General, we found the commercial models were worse than chance in identifying women of color who are at increased risk for breast cancer. This is particularly

problematic given that Black women are over 40 percent more likely to die from breast cancer, due to differences in risk profiles, age at diagnosis, tumor biology, stage at diagnosis and access to health care.

Until now, we have not had the tools to offer effective screening strategies personalized to the individual woman, regardless of race. We were excited to see our AI models didn't have racial bias, and performed better than the commercial models, and equally well across the full diversity of patients we serve.

How has your work been influenced by COVID-19?
COVID-19 reduced the number of women who were screened for breast cancer during the beginning of the pandemic. Now, we are working hard to ensure our patients at risk for and with breast cancer don't fall through the cracks. Now is not the time to "wait this out" or "go back to normal." In fact, COVID-19 has allowed us to see many challenges in our system with fresh eyes.

We were excited to see our AI models didn't have racial bias, and performed better than the commercial models, and equally well across the full diversity of patients we serve.

We asked ourselves, how can we use this opportunity to rebuild our screening programs to be better and smarter than they were pre-COVID? How can we tackle the challenges of screening the right patient at the right time, leveraging our most advanced knowledge and technology?

When the governor asked that we screen those at increased risk for breast cancer first in our early phases of reopening, a lightbulb went off. We knew if we used traditional methods we would only continue to support racially biased and ineffective methods of identifying women at risk. Why not use our AI discoveries to help us find these patients? Our AI models could identify women most in need of screening now. This process included bringing back our patients with a history of breast cancer, those already known to be at high risk, and those identified by our AI models as being at increased risk.

What are your next steps?
We are fortunate to have experts from diverse disciplines in our Mass General Brigham community to support careful implementation of our research into patient care. We have done a lot of work to advance the critical issues related to widespread clinical implementation. However, we cannot stop there. The pathway forward is clear and we are eager to advance our work by continuing to combine the powers of AI and medical imaging to further our goal of accessible, equitable health care for all patients at Mass General and beyond.

At Mass General, the most visionary minds in medicine work together to bring bold breakthroughs from the lab to our patients' bedsides—providing compassionate care and producing revolutionary results. Your support will fuel our unrelenting pursuit of medical excellence—empowering patients, strengthening communities and creating a healthier world. From making an outright gift to starting a fundraising campaign or hosting an event, there are many ways that you can help Mass General shape the future of health care. Send us an email at mghdevelopment@partners.org or call us at 617.726.2200

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Liquid Biopsy: in Detecting and Preventing Cancer: An Interview with Dr. Hai Yan, MD, PhD

Blood-based Cancer Biomarkers

Cancer biomarkers are typically molecules produced by a body's response to the tumor or by the tumor itself. They can usually be detected in the blood, and may assist in screening and diagnosis, as well as monitoring disease progression. The purpose of a biomarker for screening and early detection is to detect cancer at a stage when the cancer is curable. Screening biomarkers should be able to detect cancer before symptoms appear (which is usually associated with an earlier stage) and thereby increase survival rate. Such tests need to be highly specific in order to minimize false positives (instances where the test indicates the presence of cancer where there is none). Because of the risk of false positive findings leading to unnecessary invasive medical procedures, screening tests for cancer have often been limited in a standard health care setting. Additionally, existing biomarkers often have limited use as screening markers because of their low sensitivity and specificity in early-stage cancer and becoming more reliable as a cancer progresses. However, a few biomarkers have been used for screening including AFP for hepatocellular cancer in high-risk patients, CA-125 for epithelial ovarian cancer, and PSA for prostate cancer . Unfortunately, all three of these biomarkers can be elevated for reasons other than malignancy. AFP may be elevated due to noncancerous liver conditions, such as fatty liver or cirrhosis, or due to other types of cancer. CA-125 may be elevated for a number of reasons, even including endometriosis and pelvic inflammatory disease, and some women with ovarian cancer never have elevated CA-125 levels. Similarly, PSA has a complicated track record, as it may not be elevated in some cases with high-grade cancer, and also has a low positive predictive value. However, a continuous rise in PSA may be more indicative of a growing tumor, and extremely high levels of PSA are more likely to be connected with cancer .

Dr. Hai Yan is the Henry S. Friedman Distinguished Professor of Neuro-Oncology in the School of Medicine at Duke University. His training is in cancer genetics and he was trained by the world-renowned cancer geneticist Bert Vogelstein of Johns Hopkins.

In Vogelstein's lab, he helped to develop one of the first liquid biopsy technology, named BEAMing, which enabled the detection of rare mutations in the blood. Dr. Yan went to become a professor of pathology at Duke University, where his research centers the molecular genetics and biology of cancer, with a focus on identifying, characterizing, and developing therapies to target the major mutations driving brain tumors. Among his accomplishments is the discovery of mutations in IDH1 and IDH2 which are dominant in 70% of progressive gliomas, a common type of primary brain tumor. These mutations have also been found to be important in acute myeloid leukemia, cholangiocarcinoma, and chondrosarcoma. Since that discovery he has also worked to develop drugs targeting each mutation, which enables precision treatment for patients with IDH1/2 driven cancers.

What is a "liquid biopsy"?

Two words: liquid and biopsy. A biopsy is the traditional tool for doctors to know what a disease is. If you have a suspected solid tumor, you can use a needle to pick up some cells from inside the mass. Using a microscope, a doctor can look at the cells, and based on their structure can determine whether they are cancerous, what kind of cancer it is, and how aggressive it is. Typically, a biopsy is performed after a patient comes to a clinic with symptoms and a likely tumor has been revealed by imaging. But biopsies are invasive and can miss the cancer, resulting in a false negative result. So, researchers in the cancer field have tried for a long time to find ways to get similar information in a non-invasive way that is also highly sensitive and specific. Any non-invasive approach to finding out what the disease is by using body fluid can be called a liquid biopsy. Liquid can mean blood, saliva, urine, or even cerebrospinal fluid, for a brain tumor. A liquid biopsy, then, is a test to extract cells, or tissue, or biomarkers in a non-invasive way. The current technology can be very sensitive and specific for revealing tumors at an early state, perhaps even before they become symptomatic. This allows physicians to detect problems before they manifest and to save patients' lives.

What types of liquid biopsies are there and how are they analyzed?

It really depends on the type of liquid biopsy. For instance, a microscope is still used to analyze the cells acquired with a pap smear. The science is more advanced with other types of liquid biopsy, meaning that we use biomarkers, like DNA, RNA, or proteins which can reflect the true nature of the disease.

Blood-based biomarkers present a particular challenge for analysis. If you have a marker that shows as abnormally high in the blood, there are two questions. One, is it truly related to cancer? Two, where is the tumor located? Fortunately, we have developed technologies in the last 10-20 years that are more sensitive, more specific, and can also help us know where a tumor is located.

One technology is the identification of circulating tumor DNA or ctDNA in the blood. This ctDNA can be analyzed to detect changes that indicate the presence of cancer in the body. One way is through the detection of cancer-specific mutations. When a tumor is progressing, the tumor becomes bigger and invasive and can shed cells and DNA into the blood. Every cancer type has unique genetic alterations and also shares common mutations with other types, creating a genetic fingerprint for each type of cancer. By drawing a patient's blood and analyzing it for a genetic signature, we can detect cancer with high specificity. As an example, if you find a combination of APC and p53 mutations, that patient most likely already has colorectal cancer. However, there are still limitations, lower stage tumors are less likely to shed a lot of DNA into the bloodstream, meaning that the chance to detect low-grade tumors is much lower than the higher-grade tumors.

Analysis of circulating DNA also can be used to detect epigenetic changes. Where mutations change sequence of the DNA, epigenetic changes modify how genes are expressed without changing the sequence. For instance, methylation can change the activity of a DNA segment without changing the sequence. Methylation may inactivate or suppress "tumor suppressor genes" or it may activate oncogenes—genes that promote tumor growth. Aberrant epigenetic changes can be identified sometimes even before a tumor starts to grow, at the precancerous stage, meaning that through detection of abnormal methylation in circulating DNA, it may be possible to detect precancerous tumors. Research and clinical study are needed to illustrate whether benign lesions identified in this way can progress and cause problems.

Some companies currently use ctDNA for screening high-risk individuals for liver cancer or colorectal cancer, while a few companies are developing ctDNA technology to detect multiple cancers. Different companies are trying to use different tools, whether looking for mutations or for methylation to detect cancer, and I think in about five years we will know which techniques are the most cost-effective, most specific, and most successful.

What is the difference between ctDNA and CTC?

The mainstream method for cancer screening is cell free DNA, which is the circulating tumor DNA, or ctDNA, but there is another way. If the tumor becomes invasive, penetrating into the blood, it becomes mobile and may seed a new tumor in a different location in the body. For example, lung cancer can become invasive and may manifest as a metastatic tumor in the brain. There is a stage in the process at which the tumor cells begin to circulate in the bloodstream, and at that point it becomes possible to sample the circulating tumor cells, or CTC rather than just the ctDNA. The challenge comes in filtering out the other cells in the blood in order to capture only tumor cells for analysis. Because it is so challenging, analysis of CTC is still at a very early research stage, but as research progresses it may bring a fundamental breakthrough in cancer treatment.

What kills cancer patients is a tumor that becomes invasive or metastatic. CTC may be able to help us catch that moment when a benign mass becomes life-threatening. With that knowledge it may be possible to develop drugs to target those few metastatic cells to prevent metastasis from happening.

Currently, CTC could be used as a way to monitor cancer patients after therapy. Sometimes a tumor will become drug-resistant and may become metastatic. A metastatic tumor will be genetically and biologically different from the primary tumor and may require a change in drug treatment. Using CTC or ctDNA, we will be able see the changes and advise physicians to change treatment strategy.

What is the future for liquid biopsy?

Right now, it is generally understood that it is important to see a dentist twice a year, but most people don't have the same approach to general health. I see a future where patients undergo a general health check at least once a year. That health check would include multiple tools for early cancer screening, including liquid biopsies to identify the presence of tumors and also imaging to figure out the precise location of tumors.

6

THINGS YOU CAN DO TO

avoid cancer

1. Avoid tobacco products.

   Use of tobacco is the cause for at least 30% of all cancer deaths in the United States.

2. Maintain a healthy weight, diet, and activity level. (The American Cancer Society has guidelines for diet and physical activity to reduce cancer risk).

   Being overweight or obese increases the risk of at least 12 types of cancer and is thought to be the cause of 11% of cancers in women and 5% in men in the United States.

3. Protect yourself from UV radiation.

   Almost all skin melanomas are caused by exposure to ultraviolet radiation from either the sun or from indoor tanning.

4. Learn about the infections that can lead to cancer and how to protect yourself.

   The most common infections that lead to increased cancer risk are HPV (human papillomavirus), Hepatitis B and C, and Helicobacter pylori.

5. Get genetic testing to assess inherited risk.

   Inherited genetic traits may responsible for up to 10% of all cancers.

6. Get early and regular screening using imaging and blood tests to catch cancer before it progresses.

   Detecting a tumor early means being able to eliminate it before it causes too much harm.

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