How to Measure Health by Dan Pardi, MS, PhD - (IHMC, 2023 - Post Event Recording) Transcript

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Introduction and defining health

It's a pleasure to be at IHMC again. Let me start by telling you what I do. A main goal of my career is to translate complex ideas into more easily graspable concepts so that more of us can take part in wiser strategies to achieve better health.

My last talk was at the Pensacola location in November, 2022. That talk, was titled actual health, how to stay human in the digital age. You can find the talk by searching IHMC and Dan Party on YouTube.

The title of my talk today is Measuring Health, What Should We Measure? Since this talk is about how to measure health, we need to have a good understanding of what health is.

What is it that we are trying to measuring? While I began my last talk exploring the same question, what is health? I will start this topic by investigating the topic with even more depth.

If you saw that last talk, you might recall that I started by discussing lexical semantics and how it is the branch of linguistics concerned with word meaning.

Some ideas are easier to encircle with semantic meaning, while other concepts are more challenging. Concepts so rich, so expansive, that they seem ineffable.

For these types of concepts, definitional offerings can be so broad that the hardly mean anything at all. They have no teeth. More precise offerings, on the other hand, are easily criticizable, as we try to squeeze the large concept into a box that is ultimately too small.

Or they suffer from tautology, where the definition includes a circular reference back to itself. You define the term with the terms. In scenarios like this, you get semantic uncertainty.

where different explanations of its meaning exist, causing confusion. And yet, to quote Socrates, the beginning of wisdom is the definition of terms. If we don't have a solid definition for something, several undesirable outcomes are possible.

First, division between camps with competing ideas. Next, inefficiencies in operationalizing around the concept. Third, marginalization of key parts if other parts dominate the majority perspective in the dialogue.

Additionally, attempts to measure health may be biased towards only the portions of health that fall under the lens of the proverbial microscope. It reminds me of a parable of The Man Who Lost His Keys.

The parables goes as follows. A man is walking home one night and realizes he has lost his keys. He starts to search for them under a street lamp because it is where the light is, even though he knows he lost them elsewhere.

A passerby sees him searching and asks him where he lost his keys. The man points to a dark alley and says that he had lost them down there, but he is searching under the streetlamp because it is too dark in the alley to see anything.

Similarly, it is entirely possible that our society has constrained its understanding of health by virtue of what we can and can't measure. So keep this in mind as we enter into this discussion on measurement.

To better understand health, I'd like to introduce philosopher Christopher Boors. Boores has made significant

contributions to the philosophy of medicine.

He is famous for his biostatistical theory of Health and Disease. According to his theory, health is the absence of any statistically abnormal functioning of an organism's physiological systems.

A healthy individual, therefore, is one whose physiological functioning falls within a range of what is statistically normal for their age, sex, race, and other relevant factors.

What about disease? According to Bohr's, disease is the opposite of health. It is a presence of any statistically abnormal functioning of an organism's physiological systems.

A disease simply is not in the nature of the species. it is anything that prevents a body part from functioning normally, or interferes with the performance of some natural function, thus decreasing the chance of survival and reproduction.

For instance, a cataract is an eye disease that causes blurry or hazy vision.

Disease, illness, well-being, and welfare

it negatively impacts the functioning of this physiological system and therefore is a disease. So diseases are internal states that depress a physiological ability below a species typical level.

What is illness? Is there a difference between disease and illness. In fact, in the literature or parlance of those discussing illness and disease, there is considerable overlap between these terms and what they are used to describe.

Christopher Bors describes illness as a systemic disease affecting the organism as whole. Some use illness to mean an issue that is reversible, while a disease really isn't.

And yet in other instances, illness is used when the condition exacts a subjective negative toll, causing suffering in the individual. In contrast, some diseases may not be noticeable at all.

So an illness affects the whole person, has a significant impact on one's quality of life, ability to function, and overall well-being. Speaking of well being, it is another term often discussed with health.

or used as a synonym. In fact, in 1948, the World Health Organization defined health as not merely the absence of disease or infirmity, but a state of complete physical, mental, and social well-being.

So according to them, health is a State of Complete Well-Being. And the World Health Organization defines well-being as a state of being in good health, both physically and mentally.

So health is a State of Complete Well-Being, and well being is the state in being good in health both physical and mental. The World health organization also characterizes well beeing as the person's ability to cope with and overcome the challenges of everyday life.

Now, two types of wellbeeing are often discussed. Hedonic wellbeing refers to the cognitive evaluation of life satisfaction and a positive affect. Eudaemonic well-being is related to the determination of life's meaning and self-actualization.

I don't see health and well being as synonyms. i see them as distinct but intimately linked. Let's look at how these two concepts interact. let's Look at an aspect of health, mental health.

Mental health is the condition of the mind. And like any form of Health, Mental Health is a dynamic state of internal equilibrium. And good mental health enables an individual to use their abilities in harmony with the universal values of society.

Aside from just the absence of illness, mental heath also includes things like basic cognitive and social skills, the ability to recognize, express, and modulate emotions, The ability empathize with others, cope with adverse life events, And function in social roles.

Some researchers have argued that mental Health also include the capacity to value life and also the Capacity to engage in it. But does this feel right to you, where we have mental illness on one end of the spectrum and happiness and well-being on the other end?

We know that you can have a happy psychopath who has tendencies to live life aberrant to the rules of society. On the hand, there are circumstances in which one's mind will instantiate the properties needed for mental health but in which one's pursuit of well-being is frustrated by the wider world.

That is, they are unhappy because let's say they lost their job or are having to take care of a sick relative. So what we're really dealing with is two different scales where mental health is the condition of the mind and well being is a matter of how a person feels about their life.

So health and well-being are different things. But these two things interact and affect one another. For instance, if you take someone with attention deficit disorder, the condition of their mind has a hard time performing the needed capability of focusing.

And you can easily imagine how this would be a significant drain on happiness as this afflicted individual struggles to do their tasks efficiently in a modern environment with modern demands.

and how that situation could very likely affect how this person feels about aspects of their life. And vice versa. Mental health is not likely to endure under circumstances that are seriously detrimental to well-being.

It is easy to imagine a person developing depression after years of caregiving to a dying loved one. But we can clearly see from these examples and illustrations that health and well being are not the same thing, but important travel partners.

Welfare is another term of interest for our purpose of understanding health. It is something used synonymously with wellbeing, just like illness and disease are used.

I prefer to create a clear distinction between wellbeing and welfare so that we can use each of them pointedly. While wellbeing is about life satisfaction, positive affect, life meaning and self-actualization, welfare refers to the environmental conditions in which the health of an individual or group is occurring.

Welfare can include access to resources such as healthcare, education, housing, employment, social support, protection from harm, all of which directly or indirectly impact physiological and mental health.

Importantly, while another person cannot be healthy for you or have wellbeing for, you people can look after someone else's welfare, like a parent looking after the welfare of a child, or even a person taking care of, a houseplant and making sure it has good soil, the right amount of light and water for it to survive and thrive.

That person is looking after the welfare of that plant to ensure it is in good health. Here's an illustration of the idea of welfare in action. Let's say there is an environmental catastrophe at an oil refinery in a small town.

The catastrophe poisons the water supply, eliminates most of local jobs, and half of townspeople move somewhere else. This illustration depicts radical change in the living circumstances for these town people.

The physical environment has increased in toxicity in the water, air, and soil. There are now fewer job opportunities, which affect one's ability to attain health-related resources like healthy food.

And their social community has changed. It has shrank, And many of its remaining inhabitants are psychologically stressed, Which has a contagious quality to it.

The stress of others as a stress-inducing factor for the entire community. Therefore, the welfare of these people has been significantly altered. You would predict with great certainty that the average health of the people in this town would diminish measurably in time.

Lastly, let's look at wellness. According to the Global Wellness Institute, wellness is about making choices aimed towards optimizing holistic health and well-being.

It is not a passive or static state, but an active individual pursuit that is associated with intentions, choices, and actions. While not all humans share an equitable baseline from which our wellness efforts begin, we still have self-responsibility for our behaviors and lifestyles.

For instance, a man in jail may not have full freedom to determine the pattern of their life. But even with these restrictions, he can decide to perform or not perform push-ups in a cell in order to try to improve and maintain his own health.

Let's do a synthesis here. We've talked about health as physiological functioning and whether the measure of that functioning falls within statistically normal ranges for that person's sex, race, and age.

If there is a dysfunction, is that dysfunction system-wide, permanent or reversible, or causing discomfort or suffering? The answer to which would help determine if this is disease or an illness.

We have talked about well-being, or how a person feels their life is going, and how personal circumstances and mind-frame impact a persons' health, how that person's health level affects their well being.

We discussed a personal's environment and societal circumstances, as well as how those support well beeing or health.

Why health measurement matters

Welfare can be thought of as the condition in which one's well health is taking place. And lastly, wellness. The willful efforts one makes to improve and support their health All of these topics are really discussing health from different perspectives or through different lenses, kind of like how jogging and sprinting are talking about running, but just different forms of it.

So, with this fundamental understanding of health in mind, let's begin our discussion on measurement. Why do we measure health? to understand our health status, to find insights on things that are otherwise hard to perceive.

For instance, we cannot feel heart disease or cancer developing, and to help your healthcare team, including you, make more informed decisions about your health practice and your care.

And for some, curiosity, the desire to simply learn and know more about our body, even if you are not inquiring about something specific. Measurement is big business.

It's difficult to provide an exact number of health measurement tests that exist today because new tests are constantly being developed and existing tests updated or replaced all the time.

But there are thousands of tests currently available. In fact, the global biomarker market is estimated to be $59.1 billion in 2023, and it's projected to grow 12% year-over-year to reach a market size of over $104 billion by 2028. So the biomARKER business is big.

What exactly is a biomARKER? Simply put, a bioMARKer is any characteristic of the body that one can measure. A biomarker test that is used to identify the presence or absence of a disease or a condition is, more specifically, a diagnostic.

So not all biomARKER tests are considered diagnostics. And there are many levels to humans that we can attempt

to measure. Molecules, cells, tissue, the organs and organ systems, whole organism, and its performance.

And we can measure things like excretions, things, like urine, feces, sweat, saliva, breath, blood, and things that are in it, hormones, metabolites, proteins, lipids, sugars, etc.

Anthropometry, weight, height, waist circumference, bone density, enter adiposity. We can do imaging on the body in the forms of MRI, an x-ray, various types of scans.

We could evaluate a person's senses, their hearing, vision, smell, taste, and touch. we could do various functional tests on somebody, from a max effort cardiovascular test to muscular strength to a psychomotor vigilance test, a test of memory.

You can look at other things, temperature, blood pressure, hair samples, skin elasticity, we can a biopsy of tissues. and we could do questionnaires about a person's feelings, their opinions, attitudes, perspectives, and recall.

This is not really what we measure but how, but we can also then do omics, which is looking at lots of data on various types of systems like your biome, genome, epigenome etc.

If you recall Christopher Bohr's definition for health and disease, health is the absence of any statistically abnormal functioning of an organism's physiological system for their age, sex, race, and other relevant factors.

And disease is opposite. It's the presence of a statistically normal functioning. Therefore, for each individual thing we would like to use to measure health in some way, we must first establish normative values so that we can make sense of the information.

and that is not an easy task. Yet, doing so is a valuable endeavor. But normality itself, however, is an challenged concept, especially when physiological norms and societal norms are considered at the same time.

We can use the example of smokers to illustrate what I mean. If everybody smoked, it would be sociologically normal to smoke, in the sense of being common.

Given that risk calculations look at deviations outside the normal range, the behavior of smoking would not be considered risky. Despite this sociological calculation, smoking will remain physiologically abnormal and therefore risky when calculated in a non-smoking population.

Additionally, deciding on what is normal may become increasingly problematic if normal ranges are calibrated against an increasingly sick population like we are seeing in many modern societies.

This is one of the reasons why we're so interested in measuring health in natural living, modern-day hunter-gatherer societies like the Chimane of Bolivia and the Hadza of Tanzania.

In some ways, measurement of these people may represent truer values of human health than the ones calibated against already modernized samples. Now, when assessing risk, we create ranges.

And a figure tucked just inside the normal risk range, but only a point away from the disease category, has the same calculated risk as the figure that is farther from a diagnostic cutoff.

So, while the calculation might be statistically true, it might not be clinically true that these two individuals have the risk for an outcome. I mention this as preamble to ask, how do we determine optimal?

Biomarkers, norms, and validation

It's possible we just haven't prioritized that historically when we were mostly concerned with determining frank borders for the purpose of making a disease diagnosis so that our medical system could treat it.

But what you would imagine an optimal range to be is a narrower range within the normative range. That statistically would show to differentiate on certain outcomes between the rest of the values in the normal range Now, an adult can assess their data against ranges and figures in various ways.

We can look at ranges established in healthy people in their demographic community for age, sex, and race, or even against their own personal historical figures.

This type of comparison can be used to calculate an adults' youth span or their preservation of function from categorical or personal peak values. The idea is exploited by the company Qbio, who does a comprehensive scan of all body systems and repeats those scans every so often to create a longitudinal record of your biomarkers over time.

Because everyone is unique, they feel that a within-person comparison is the best way to measure oneself. Lastly, novelty challenges standard reference ranges.

If one adopts, let's say, a novel diet, and in response a biomARKer is elevated, but stable, does that elevated value indicate risk the same way it does in the reference class upon which risk was originally based?

Does, for instance, a higher LDL value carry the risk in context of a ketogenic diet than it did in a typical Western diet? But when faced with a situation like this, it seems prudent to me to assume that an aberrant score does imply elevated risk until proven otherwise.

But you will often see advocates of a new position use a form of sleight of hand, saying that, an Aberrant Score is not risky because of X, Y, and Z. That might be true, but we need time to work that out and we don't want to make casual assumptions when it comes to people's health.

So we rarely measure disease directly. Rather, we collect biomarkers and see what ranges they fall into so that we can attempt to predict the future. Most often, this is a multi-step approach.

In clinical medicine, our healthcare system cannot afford to give everyone the most thorough and expensive test as a screening tool. Additionally, more thorough tests often come with additional risk to the patient, as they can be more invasive.

Therefore, for both cost and safety, a quicker and dirtier measurement happens first, and if that test indicates a possible issue, now this merits the use of the more expensive, riskier test.

which will hopefully give you a clearer picture of the situation. But mainly, we are using biomarker values to try to predict the future. How does this happen?

There are a variety of approaches, but one of most common ones is for scientists to conduct experiments controlling variables and measuring specific parameters.

From there, mathematical and statistical models are used to extrapolate trends and patterns observed in the data to then draw associations to specific outcomes.

And now, with techniques such as machine learning and bioinformatics, scientists have been able to increase the predictive value of biomarkers to better identify disease outcomes, drug responses, and other biological phenomenon.

It's important to note that predicting future outcomes in health is a dynamic process. It involves constant refinement and ongoing validation as new information emerges and as techniques to evaluate data emerge.

Let me give you an example. Recently, I had a conversation with Professor Pankaj Kapahi from the Buck Institute on Aging for my podcast, Humanoids Radio.

He and a team from Google Health and UCSF recently published a paper on a biological age clock that is measured through the human eye. I'll discuss biological age clocks more in the next section, but the point I'd like to make now is that they use deep learning AI models on hundreds of thousands of eye records from various databases.

And the AI model was able to predict outcomes that weren't possible before, including measurements of biological ages. One of the most interesting parts of that conversation with Professor Kapahee was when he mentioned that he didn't know how the A. I.

was making its predictions. That is one of the crazy parts about AI. At times, we can train it to do an even better job than the best human experts, but we don't often know how it's doing what it is doing.

But the promise here is that we feed future AI models mountains of data from populations and then all of your own health data, and perhaps it will be able to make some insightful predictions that were impossible to previously.

In regard to testing, accuracy and precision are two fundamental concepts used to assess the performance of a health biomarker. An accurate biomarken provides results that are in close agreement with the actual value.

In other words, it assesses the degree of correctness or trueness of the measurement. Accuracy is typically evaluated by comparing a biomarker measurement to a gold standard or reference method, if available.

And precision measures the reproducibility of the repeated measures of that same biomaker under identical conditions. A precise biomARKer produces consistent results when measured repeatedly.

It's worth noting that a biomarker can be accurate but imprecise, producing results that are consistently far away from the true value, or precise but inaccurate, produce consistent measurements that consistently biased away form the truth value.

Therefore, in order to have a reliable biomarquer, it's essential to see adequate accuracy and precision when assessing its performance. A reliable biomarkers is a trustworthy biomaker.

I'd like to return to this idea about precision. Identical conditions doesn't just mean the lab room in which it was tested, but it also means things like time of day.

For any test, I'd like to see two additional tests done in the process of validation. First is the 24-hour assessment, meaning that you would assess that biomarker approximately every hour or so across a 24 hour period.

Does the variable in question naturally fluctuate across the day? Second, does the variable in question naturally fluctuate from day to day? In both of these cases, a change between measurement one and two might be interpreted as a clinically meaningful delta, when really the difference just reflects the natural and helpful variation of that marker in questions.

If there is natural fluctuation in variable across a day, then the testing instructions should ensure that the test is taken at the same time every time it is administered.

Now, what to do if there's natural variability from data day. It would be ideal to collect daily data for a period of time, then look at the variability under normal circumstances of living.

That is not always done in the validation of tests, and it's one of the reasons why periodic measurements of certain biomarkers are hard to interpret or have a wider standard deviation range.

For these types of situations, you might only be confident that there is an issue worth investigating if the score on the second measurement is vastly different than the scores on test one.

So, the process of connecting a biomarker to an outcome is part of the biomarken's validation process. The goal of

a diagnostic test is to determine whether the biomarkers can accurately distinguish between affected and unaffected individuals, a biomerker has predictive value when it can reliably distinguish outcomes of people with different scores, and part being reliable means that the performance of this biomaker must show adequate accuracy and precision.

It's further useful when we know natural within day variability and day-to-day variability of the biomarker question so that we can make sense of their return values.

Now, if a biomarker has enough supporting evidence behind it, it may receive regulatory approval from governing bodies like the FDA, allowing it to be used as a diagnostic tool for patient management and standards of care.

Lastly, there's also adoption in the form of clinical adoption. Do doctors use it in their clinic? Research adoption? Do scientists use in in studies?

And commercial adoption, do people buy it if they can buy directly without a doctor's prescription? But I must say that commercial option is often predicated mostly on marketing and that can be problematic.

So with these important foundational measurement concepts behind us, let's move on to part three on actual measurements. The most traditional use of biomarkers is for diagnostic purposes.

And of course, this style of use makes great sense. We want to identify possible existential risks. According to the World Health Organization, the top 10 leading causes of death globally in 2020 were ischemic heart disease, stroke, COPD, lower respiratory infections, Alzheimer's disease and other dementias, lung issues, diabetes mellitus, kidney disease liver disease.

And digestive diseases. In part two of this talk, we discussed how most diagnostics follow a screen first, deeply investigate second methodology. and how that makes sense from the perspective of cost, patient risk, and time.

For each of the various killers, different tests can be done for various systems in the body. for time purposes, we will highlight only two, cardiovascular health and liver health.

What are some common medical and lab tests to evaluate the health in functioning of a cardiovascular system?

Diagnostic testing and biological age clocks

Screening can include a lipid panel, cardiac enzyme tests, NT Pro BNP tests or natriuretic peptide tests which measure the level of a protein that can indicate heart failure, electrolyte panel complete blood count or CBC, coagulation panel and erythrocyte sedimentation rate or ESR which measures the rate at which red blood cells settle in a test tube which can indicates inflammation in the body.

If there's an issue detected in the screening, a secondary evaluation can include electrocardiogram, an echocardiogram a cardiac stress test, cardiac catheterization, CT angiography, and others.

Now to monitor liver health, liver functioning tests are a group of blood tests to evaluate aspects of liver healthy. These measure enzymes and proteins produced by the liver, such as alanine transaminase, aspartate transaminase alkaline phosphatase total bilirubin, gamma glutamyl transferase and prothrombin time.

If there's signs of an issue from the screen, a secondary evaluation may include imaging tests that check for liver damage or disease, as well as the size and texture of the liver.

These include ultrasound, CT scans, MRIs, or even a biopsy to check the histology of liver So you get the idea. these diagnostic strategies are looking at specific organ systems in a two-step fashion dependent on need.

But is there a way to assess the health of a whole person? Well, the Holy Grail in measurement has been the ideal that we could identify a single measurement of person's health.

The idea of biological age has served this role. It wasn't until the mid-1970s that the term biological-age was coined by scientist Thomas Kirkwood. He defined it as the age of an organism as estimated from its physiological or biochemical state.

Simply put, biological ages refers to the amount that one has aged in the years they have lived. Some people age more slowly, and some people aged faster.

Here is a graphical representation of the idea. We see an image of a man and a woman representing the average age of cohort. On the left, we have the slowest aging members.

And on the right, We have 10 fastest aging cohort members Now remember, these people were all born on that same day. They are the same chronological age.

While you can see clear differences between each grouping, the differences are quite stark when comparing the slowest and fastest aging samples. An accurate measurement of biological age should be valuable.

It could serve as an indicator of overall health, provide insights into an individual's risk for age-related diseases, would provide an accurate signal of one's mortality and longevity probability, and would enable cost-effective quantification of any potential rejuvenation therapy.

This could serve as a replacement for time-consuming and expensive lifespan studies. You see, humans' long lifespan makes it prohibitively time consuming to test whether a treatment extends health span or lifespan.

What is needed as way to measure each clinical trial participant's personal pace of biological aging before, during, and after a study and at long-term follow-up to test whether a geroprotective therapy slows that pace and whether the benefits last.

Having this could enable us to make much faster progress in determining where to place our focus and efforts when it comes to affecting the aging process.

Biological age can be estimated using various biomarkers to provide information about an individual's cellular and molecular health, which can also be used to calculate an estimate for a person's biological age.

There are actually many science-based tests and biomarkers that have been proposed as potential clocks for estimating someone's biological age. These include telomere length tests, facial scans, tests of one's microbiome, and as I mentioned previously with Professor Pankaj Kapahi from the Buck Institute, now there's even a retinal clock called IH.

But the clocks that've received the most attention in the last 10 years are epigenetic clocks. Let's take a look at those now. Epigenetics is the study of how our genes can be activated or silenced in response to the environment, including from diets, stress, temperature, sun exposure, toxins, and more.

Epigeneric changes can pass down from one generation to another and can have significant impact on our health and well-being. DNA methylation is a form of epigenetic regulation.

And a person's DNA-methylation status changes as we age. and as we are exposed to various environmental factors. So by understanding epigenetics, we can gain insight into how our lifestyle choices can affect our genes' expression patterns and how we're aging.

Launched in the early 2010s, We saw the first generation of epigentic clocks. The Hanoum clock, named after researcher Gregory Hanum from UC San Diego, analyzed 71 CPG sites from DNA obtained from blood.

And the Horvath clock named After researcher Steve Horvathe from UCLA, considered 353 CBG sites from multiple tissues. Both clocks managed to accurately predict a person's chronological age with high accuracy.

Funny enough, the Hanoum biological clock was discovered serendipitously. In a lab discussion, Greg Hanum said, guys, I just can't find any cancer signal when analyzing my epigenome data.

You know why? Because a persons age is such a pesky covariant. So many of the methylation marks just track age, and I can get rid of that signal. The lab group all paused and said, you know, that's interesting.

So this is how they discovered that age could be predicted by looking at the markers on the epigenome. But these clocks correlated strongly with chronological age, but weakly with biological age and clinical measures of aging diseases, such as high blood pressure.

In 2018, scientists started to develop what we call second and third generation epigenetic age tests. These were meant to improve morbidity and mortality predictions.

The newer generation epigenetic clocks are good health predictors, or at least as good as any standard lab tests currently used in clinical settings like LDL, HbA1c, creatinine, etc.

Second generation clocks have been trained on other age-related measures, including a Phenotypic Biomarker of Morbidity, or PhenoAge, and Time to All Cause Mortality, GrimAGE.

DNAM PhonoAGe. This test was developed by Morgan Levine and her team at Yale University. It is based on DNA methylation patterns and includes 513 CPG sites that are associated with age related phenotypes.

This test has been used to be a better age predictor of mortality and morbidity than chronological age or first-generation epigenetic tests. Grim age.

This was developed by Steve Horvath and his team at UCLA. It is based on DNA methylation patterns and includes 1,035 CPG sites that are associated with mortality risk.

The grim age test also includes additional biomarkers such as smoking status, lung function, and serum levels of proteins associated The Grimm age test has been shown to be a better predictor of mortality risk than other epigenetic age tests, with up to 96% accuracy.

One of the most advanced clocks available today is the Dunedin pace clock. What is Duneden paceclock? It stands for pace of aging calculated from the epigeno.

To create this clock, the researchers used data from Dunedean study, 1972-1973 birth cohort. Duneedin, by the way, is a town in New Zealand. They tracked within individual decline against many indicators of organ system integrity and body functioning across four time points spanning two decades to model pace of aging, or in other words, the ongoing rate of decline in system.

They distilled this into a single time point DNA methylation blood test, and then validated the clock against five additional data sets. And the results of this endeavor have been impressive.

First, Dunedin pace is distinct from DNA methylation clocks in both theory and method. It provides an estimate of the pace of aging, which again is the ongoing rate of decline in system integrity.

It showed high test retest reliability. it is precise and has stronger associations with signs of ageing. For instance, it has strongly associated with morbidity, disability, and mortality.

And it showed faster aging in older people, Which we know is true. Older people age faster than younger people. and this test detected this. And it showed faster aging in young adults with childhood adversity, showing the negative impact of stress on accelerating the aging process.

So I'd like to walk through a concept here. Epigenetic age is theoretically measuring the accumulated damage of aging. Let's look at a fictitious example of a man named Peter.

Peter's a 54 year old man living in Southern California. In his 20s and 30s, he maintained an unhealthy lifestyle. He did shift work, He smoked a pack of cigarettes a day, didn't eat well, and didn' exercise.

And that pattern of living caused him to age faster in this time window. But in his mid-40s Peter started taking better care of himself, And because of this, his pace of aging slowed.

Now, if Peter got an epigenetic age test, it might tell him that he's two years older than his chronological age of 54. This is due to how he lived when he was younger.

But if he got a pace of aging test, it might tell him that he's currently aging only 10 months out of every year. You see, his current pace aging is slower, even though his biological age calculation is older.

If he just got an epigenetic age test that might take the wind out his sails. He might think he is doing things wrong and would give up on his healthy habits when really he currently doing thing right.

So, do need and pace is a good test, but researchers believe there's still room to improve the accuracy of epigenetic clocks based on patterns of DNA methylation.

At this time, there is no specific date for the launch of fourth generation epigeneric clocks, But research in this area is ongoing and constantly evolving.

And it's likely we will continue to see development in the field for coming years. This is an exciting area, and it feels like we are making rapid progress here.

Yet, at the same time there are many issues still in space. While there are numerous tests currently being commercialized, many researchers believe that the field is not ready for that, that these are better research tools for studies and not yet ready individual meaning.

Let's take a look at some of the concerns.

Limits of clocks and multidimensional health

Epigenetic age does not equal biological age. Technically, no measure will ever be equal to biological. It is an impossibility. Biological age, as Professor Morgan Levine calls it, is a latent concept.

A latent concept is not directly observed, but it is inferred or estimated from other variables that are observed or directly measured, and epigenetic clocks are measuring only one phenotype of aging.

So keep in mind, these clocks aren't interchangeable with biological age. We don't understand how specific epigene marks connect to the underlying process of ageing.

They do not capture all the dimensionality of real biological aging. For instance, epigenetic clocks do no capture senescence, which has shown to be important in the aging process.

Therefore, Epigenic clocks are incomplete. And a given measure of aging may or may not be less sensitive or overly sensitive to the result of a therapy that only addresses one mechanism of ageing.

We also know that aging rate is tissue specific. So attaining one score for a whole organism has challenges. If you average all tissues for a score, some tissues will be more aged than others.

This is why not all people with heart disease also have diabetes or cancer. If it was a single aging rate, we would expect equal risk for all of these age-related diseases in an individual.

So we may need to split these clocks apart, identifying age and aging rates per tissue type. And that weakens, but doesn't eliminate, the value of a universal health score.

Currently, we have no idea if changes to epigenetic age through some intervention will equate to changes in risk. And we also know that these tests may be too sensitive to your current inflammation status.

Keep in mind, lots of things can transiently increase inflammation, including exercise. But chronological age is regularly used in clinical decision making, and it's a valid endeavor to see if we can improve upon that when dealing with a specific individual.

So here with measures of biological age, you can never be exact, but over time, with great refinement of our methods, including the use of artificial intelligence, we will likely get closer and closer to a true biological age score.

It's likely, however, that to do so, we'll have to use multiple measures, not just a single one. So, multiple clock tests, functional tests structural tests imaging, etc.

Now remember, when we are measuring health, We are not often measuring it directly, but rather we're predicting it. Therefore, a good measurement of health is one that has good predictive value for future outcomes.

In that regard, we don't need to limit our investigation to objective physiological measures. Rather we can look at other factors that relate to a more comprehensive assessment of health to determine a better measurement for health.

After all, humans are complex biological systems. Therefore, human health is best understood as arcs or trajectories instead of as a static state. A health measurement indicating low health today might not yield the outcome that the static measurement would predict.

Humans can change the circumstances in which we live, altering the trajectory towards various outcomes. And sure, one way to do that is to have good information on your state today, but it's not the only way affect your future.

That is why my last talk at the Institute for Human Machine Cognition, I introduced the concept of the Health Performance Expert or HPE. This role would be like a primary care doctor, an expert generalist, but on the health training side of health.

And this role will help train individuals across the lifespan on how to live healthier. So if you'd like a more thorough description of that idea, please see my talk from the Institute of Human Machine Cognition from late 2022. Now, I do believe that these new biological age tests can usher in a new era, not only to get you to do things that we understand to be healthy, but to find novel ways to help us age better.

This can be in the form of lifestyle strategies and possibly in form interventional compounds or multidimensional therapeutic systems. There's interest to see what actually does and doesn't work to affect the aging of our physiological systems, at least from the vantage of different tests and what they can and cannot measure.

So, let's pan out and synthesize our thoughts here. We can categorize measurement into narrow and broadly focused. A narrow focus is looking at the presence or absence of a disease or an illness.

Broadly focused, we can look at markers of wellbeing, like life purpose, happiness and joy, self-actualization, and resilient mind frames. Also broadly focused, we can look at welfare.

We can take measurements of local environmental toxicity, healthy food access, personal and community safety, economic stability, sick care, and education.

And of course, wellness. we could look measurements health literacy. Has this person had skills training or mindset training? Have they undergone identity development or motivational refinement training, have they been trained on how to design their local environments or how too properly monitor and track health, et cetera, So the best picture of health should always aim to be more complete.

And I'd like to conclude with a few ideas. First, with this quote from Peter Drucker, management consultant and

winner of the Presidential Medal of Freedom, what gets measured gets managed.

This idea signifies that if you're measuring something, you are more likely to attend to it to maintain a positive score. That can be a good thing, but it can also serve as a warning.

What aren't we focusing on? Also keep in mind, not everything that can measured matters. But also, Not everything that matters can be measured. And lastly, I'd like to quote Goodhart's law.

Charles Goodheart is a British economist who is credited with expressing this core idea in the adage in a 1975 article on monetary policy in The United Kingdom.

The idea is that whenever a measure becomes a target, it loses its value as a The way to counteract this is to use multiple measures to evaluate a big complex issue, so that it is harder to game the system.

So our future of measuring health is not likely to come from one measure, but from the intelligent integration of multiple measure to yield a multidimensional understanding of your health in that moment.

Based on a solid understanding your of health situation, you can make intelligent strides to optimize your own personal path forward. And with that, I'd like to thank the IHMC for having me back to speak.

And I would like thank all of you here for your time and attention. I'm happy to take questions.