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In search of best practices for Longevity Clinics

Contents

Foreword

Amidst the myriad challenges facing humanity today, one often overlooked is the rapidly aging population. Coupled with declining birth rates, aging societies could precipitate a severe global economic crisis within the next 20 to 30 years. While this timeframe may seem distant, proactive measures are imperative to avert this impending threat.

The current healthcare systems and societal lifestyle norms belong to a bygone era characterized by assured pensions and public healthcare responsibility for individual well-being. Moreover, the adoption of these outdated systems by many developing countries, shortly before the need for reform became apparent, exacerbates the looming economic repercussions. The financial burden of maintaining the status quo is immense, posing a significant threat to global economic stability.

We need urgent, new ways of organizing healthcare to prevent a potential aging population crisis. While people live longer, the number of years of health does not proportionally increase. Instead, a growing number of individuals are afflicted by debilitating age-related chronic conditions, spending their final decades in poor health. Without intervention, this trend threatens to overwhelm the medical system, state economies, and society at large.

Healthy longevity medicine has been trying to address the problem of aging populations by helping people live longer in good health so they can stay independent, well, and active community members until old age. However, the healthy longevity medicine field is often perceived as controversial by the general public and some medical organizations. The field is not an official medicine branch, and due to a lack of regulations, there are no guidelines for practitioners. Consequently, the lack of consensus among experts in the field has led to a range of interpretations and public perceptions, such as the association of longevity medicine with promoting the prolongation of lifespan. However, contrary to these misconceptions, longevity medicine's primary focus is not to extend lifespan but „healthspan," thereby, years of life in health. Extending healthspan can enhance the quality of life of people of all ages while guaranteeing seniors healthier, more active, and fulfilling lives. Enabling people with more years in health has a massive potential to reduce the cost of treatments and care.

On the 8th of December 2023, the Buck Institute for Research on Aging hosted a meeting that gathered the healthy longevity medicine community, including longevity clinics' representatives, for the first time. The aim was to lay the groundwork for official recognition by medical bodies and establish regulations defining the scope of longevity clinics. This landmark event, known as the First Longevity Clinics Roundtable, brought together leading longevity experts and institutions to foster collaboration, share knowledge, and formulate standards and guidelines for the field. The Roundtable heralded a significant milestone, signaling progress toward broader acceptance among medical authorities and the public. This paper seeks to summarize the insights from the Roundtable, offering an initial framework for defining the concept of a longevity clinic.

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Gil Blander, PhD, InsideTracker

Owen Phillips, PhD, BrainKey

Nikolina Lauc, GlycanAge

Ryan Smith, TruDiagnostic

Sean London, MD, Prenuvo

Preface

The First Longevity Clinics Roundtable was a milestone event, bringing together leading longevity scientists, clinic representatives, diagnostics providers, and other experts for the first time. It was a gathering of specialists currently building the foundations of the burgeoning longevity field. The Roundtable represents a significant step forward in shaping the future of the sector of medical clinics focused on longevity.

The event was co-organized by the International Institute of Longevity and the Buck Institute for Research on Aging. The International Institute of Longevity is a global organization that serves as a pivotal platform for longevity clinics, investors, and technology providers. It focuses on identifying trends, sharing knowledge, and engaging in discussions related to age science, the longevity economy, and preventative healthcare. The Buck Institute for Research on Aging is a leading research institution dedicated to unraveling the mysteries of aging and age-related diseases. Located in Novato, California, it is a global hub for scientists and researchers striving to extend healthspan and improve the quality of life for aging populations.

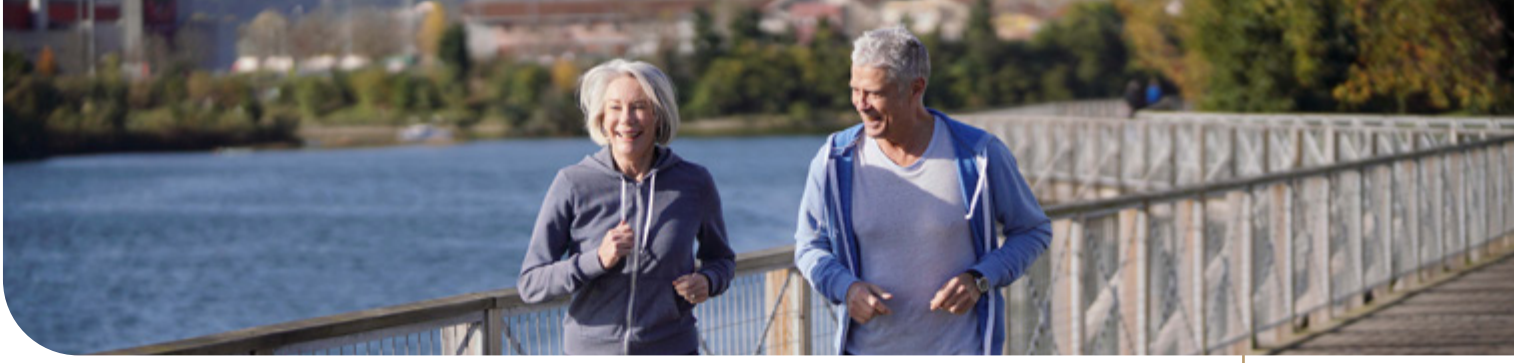
The Roundtable gathering sought to assess the current state of the market, share expertise, and identify best practices in healthy longevity medicine diagnostics and interventions. By bringing together practitioners and renowned researchers, the conference facilitated mutual exchange, enabling the identification of needs and solutions to enhance the efficiency and effectiveness of healthspan extension efforts. Steps were discussed toward establishing healthy longevity medicine as a credible field akin to established disciplines such as gerontology or cardiology. Through the establishment of a recurring forum for leading longevity clinics, the Roundtable endeavors to promote global collaboration, share innovative approaches and identify effective diagnostics and interventions to extend healthspan and improve quality of life.

Executive summary

While longevity science remains a new field, and most of the developments are theoretical or based on animal models, experts in the field already recognize the urgency of developing effective solutions to extend healthspan. More and more medical professionals realize there is a gap between promising discoveries of longevity science and an offer of conventional medical care. Recognition of the market gap propelled them to open longevity clinics – medical centers that take research findings on prolonging healthspan and try to incorporate them into comprehensible diagnostic and intervention packages.

Longevity clinics play a pivotal role in translating theoretical developments into practical applications, leveraging findings from longevity science alongside evidence-based diagnostics and interventions, as well as experimental solutions and emerging technologies. These clinics have already demonstrated success in optimizing health, preventing diseases, and extending the healthspan for their clients. The success of the first health optimization centers and longevity clinics, such as the Human Longevity, Fountain Life in the US, Longevity Center in Europe, and Chi Longevity in Singapore, has led to the establishment of more longevity clinics worldwide. However, as the field expands, collaboration and the establishment of standards, guidelines, and broader approval by official medical bodies are essential to ensure that the actors in the field are aligned with the idea of evidence-based medicine and do not fringe to more futuristic ideas.

This paper was framed based on the presentations and panel discussion from the Longevity Clinics Roundtable. The document provides a groundwork for the definition of longevity clinics. We describe the standards of established, existing longevity clinics and underscore the distinction between institutions that offer similar solutions. We lay down the current status of the biological age biomarkers, the measurement that distinguishes healthy longevity medicine from the other medical branches. Additionally, we described current steps taken toward broader recognition by medical regulatory boards and steps aiming at increasing understanding by the general public. Finally, we provide insights into the future of longevity diagnostics, interventions, and the whole field.



What is healthy longevity medicine ?

Healthy Longevity Medicine is based on longevity science which has its roots in gerontology and gained momentum in the 1930s, marked by pivotal research on caloric restriction and its impact on lifespan [1]. Since then, significant discoveries have been made, enhancing our understanding of the aging process and achieving biological age reversal in mice [2]. While geroscience primarily focuses on unraveling aging processes and strategies to slow down or reverse them, healthy longevity medicine emphasizes evidence-based solutions for patients seeking to optimize their health and extend their healthspan. Healthy longevity medicine aims to optimize health by counteracting aging processes across the lifespan.

Longevity healthcare has emerged as an alternative to the prevailing medical paradigm centered on disease treatment. The inherent issue with the traditional, often referred to by longevity specialists as a sick-care model, lies in its reactive nature. In this model, the interventions are applied when a patient becomes clinically sick, typically at a late stage in a disease that has been incubating and progressing for years. At such a late stage, significant damage has accumulated, counterregulatory mechanisms are abundant, and a true return to health and wellness is often impossible. Consequently, patients frequently find themselves reliant on medications that target the manifestation of late-stage disease until the end of their lives or in need of continuous, costly treatments. The sick-care system is severely strained, unable to adequately manage the escalating number of individuals falling ill. According to Dr. David Karow, President and Chief Innovation Officer of Human Longevity, a significant proportion—25% in the US and 33% globally—of those reaching the age of 50 years will not live to 75 years.

Healthy longevity medicine professionals suggest that the solution to the failing healthcare system is early disease prevention and the sustained maintenance of wellness. The field aims to enhance a healthy lifespan, so living for longer in good health. By keeping the majority of people well for longer, fewer people will require expensive and life-disrupting late treatments.

Nevertheless, a significant challenge facing longevity is the need for more evidence-based studies to validate treatments. Unlike conventional medicine, which relies on diagnosing and treating symptoms and conditions, longevity medicine lacks approved biomarkers endorsed by regulatory bodies to evaluate longevity treatments. However, despite the nascent stage of the field and the requirement for official approval from medical and regulatory organizations for many discussed solutions, numerous medical centers already offer longevity solutions. These medical centers call themselves longevity clinics, and their offers include treatments inspired by geroscience.

What constitutes a longevity clinic?

Healthy longevity medicine is still a new field, and consensus on the precise definition of a longevity clinic still needs to be reached. According to some experts in the field [3], what sets longevity clinics apart from other medical centers is the emphasis on measuring biological age. Biological age is a measure of an individual's age as determined by physiological markers and cellular health rather than the number of years they have lived (chronological age). It provides insight into an individual's overall health and aging process, often indicating variations from their chronological age.

However, a survey conducted by Longevity Technology [4] across 51 clinics that sought to find commonalities in their approaches uncovered a diversity of perspectives on biological age measurements and other methods. Only 47% of respondents agreed or strongly agreed that longevity clinics should measure biological age. Despite this variance in agreement, a substantial majority (72%) of clinics utilize biomarker panels to assess clients' biological age.

The survey indicates that there is only a broad understanding of the term longevity clinic. The absence of standardized regulations and guidelines has led to the widespread use of the term ‚longevity clinic,' sometimes by centers prioritizing preventive or aesthetic medicine over the application of longevity science to enhance healthspan.

Despite the ambiguity, most medical longevity clinics follow a similar client journey model. Initial comprehensive health assessments are commonplace, encompassing medical history reviews, evaluations of physical, emotional, and psychological health, along with assessments of hallmarks of aging and biological age tests. Many clinics boast proprietary assessment programs; for instance, "Fountain Life" offers its ‚150GB Upload' program, integrating imaging, genetics, and blood diagnostics. Similarly, the European "Longevity Center" provides the ‚Longevity Health Check-up,' incorporating epigenetic testing, mitochondrial assessments, blood marker analysis, and multiple biological age measurements, among other diagnostics.

Following these assessments, clients are presented with personalized action plans comprising recommendations for lifestyle modifications, potential interventions, and suggestions for re-testing to gauge the efficacy

of the interventions and changes. While some clinics offer guidance through health coaches, others enroll clients in longer-term programs involving regular check-ups and consultations with doctors. Reassessments at the conclusion of intervention programs are common practice, often relying on biological age measurements for evaluation.

Longevity clinics distinguish themselves by prioritizing preventive care, pinpointing the crucial moment of transition between wellness and disease onset, and implementing treatments aimed at mitigating or eliminating early risk factors and mitigating further disease progression. Another defining characteristic of this field is its emphasis on clinically validated lifestyle interventions that minimize the risk of prevalent diseases.

Additionally, biological age measurements are a notable departure from traditional medical model assessments. Unlike the binary healthy-or-sick evaluation typical of sick care, healthy longevity medicine endeavors to reduce or even reverse biological age, thereby optimizing overall health. Many diagnostic tools and interventions utilized by longevity clinics stem from cutting-edge research and are not yet standard in mainstream medicine. Numerous centers actively engage in research, leveraging client data analysis and forging partnerships with academia and industry.

What also makes healthy longevity medicine special is that the field embraces the latest technological advancements, leveraging big data, artificial intelligence, machine learning, and artificial intelligence's Large Language Models. There is a burgeoning trend towards decentralized studies involving clientele from longevity clinics and other non-academic cohorts, often leveraging data from wearable technology. Commercial solutions, including diagnostic tests and data analysis platforms, are utilized by most centers. Longevity clinics support the collection of patient-generated data from home, recognizing its value in providing longitudinal insights into intervention outcomes.

A unique departure from the conventional medicine nomenclature is calling people who sign up to longevity clinics "clients" instead of "patients". The name "client" implies that a person who wants to use the services of a longevity clinic can be healthy. You do not need to be a patient treated for a particular sickness to benefit from the longevity programs. The name "client" also suggests more autonomy – doctors usually consult diagnostic and intervention offers with their clients and often co-create solutions that are personalized and adjusted to lifestyle.

The typical client of a longevity clinic comprises middle-aged individuals, with gender ratios generally balanced across most clinics, although some attract a higher proportion of male clients. Clients exhibit diverse motivations for seeking out these services. Many are driven by a desire to enhance or maintain cognitive or physical performance, while others are concerned about their family medical history and the potential predisposition to conditions such as cancer, cardiovascular disease, or Alzheimer's disease. Some individuals arrive at longevity clinics with unresolved health issues that have not been adequately addressed through public healthcare channels. Client goal setting varies, with some prioritizing short-term improvements and others aiming for long-term benefits.

Longevity Diagnostics

The goal of diagnostics in longevity clinics is to develop a comprehensive understanding of each client's health.The best practices advocated by some longevity experts involve the adoption of a systemic approach, viewing health issues as stemming from imbalances across multiple systems rather than a single root cause. This approach is recommended to facilitate better diagnosis and enable health optimization, ensuring that physiological, emotional, and social systems operate optimally.

Healthy longevity medicine a wide range of diagnostic tools, from preventive precision medicine to functional medicine or AI-driven methods. Current best practices in the field are built upon:

- **Anamnesis** – Some may find it surprising to see this diagnostic tool on the list, as anamnesis is the core of conventional medical visits. However, understanding a patient's medical history is paramount. Many longevity clinics employ proprietary versions of anamnesis, conducting comprehensive initial sessions with detailed inquiries into medical history, lifestyle patterns, and individual needs and motivations.

- **Precision imaging methods** – Many centers employ precision imaging techniques such as DXA, CT scans, MRI, or ultrasound. Very often, the imaging from the equipment is either AI-powered or further analyzed by AI. Interpretation of results may involve expert analysis or utilizing commercially available platforms to generate reports based on imaging data.

- **Biological phenotyping** – This approach delves into how an organism's genetic makeup interacts with its environment to produce observable traits. Clinics utilize biological phenotyping, so observable characteristics of an organism, encompassing whole genome analysis, microbiome profiling, epigenetic assessments, hormone evaluations, and comprehensive blood panels.

- **Clinical phenotyping** – This type of phenotyping aids in identifying individuals at elevated risk for specific diseases based on clinical characteristics. Many clinics incorporate metrics such as V_{O2} max, arterial stiffness, or eye health assessments to stratify risk profiles.

- **Digital phenotyping** – Integrating data from wearables, continuous glucose monitors (CGMs), and other trackers provides longitudinal digital insights into specified health variables, such as heart rate, enabling personalized monitoring and intervention strategies.

- **Sleep assessment** – Sleep is crucial for health and can be affected by multiple factors, including age [5]. Longevity clinics pay a lot of attention to the quality of sleep and assess it systemically. The most popular methods of assessment are wearables such as wristbands or rings, pulse oximeters, and sleep EEG headbands.

- **Evaluation of physical performance** – Physical performance is an excellent measure of longevity. Higher muscle mass and higher aerobic capacity are both correlated with improved health and longevity [6]. The most popular assessments of physical performance are V_{O2} max, posture analysis, grip strength, or longitudinal HRV.

- **Nutritional assessments** – Nutrition can modulate not only health but also the aging process [7]. Therefore, longevity centers often offer an optimal, personalized diet plan. To arrive at such a plan, clients are tested via nutrigenomic, microbiome, or nutritional intolerance tests. In most cases, such assessments are performed by longevity-trained dieticians.

- **Psychological assessments** – These assessments test the client's emotional and stress resilience, social life well-being, and cognitive health.

- **Systems assessments** – Some clinics check patients' health from the perspective of physiological systems to ensure that they function optimally or are at risk of future problems. Many clinics test the following systems:

    - Cardiometabolic
    - Mitochondrial
    - Detoxification
    - Microbiome
    - Metabolic
    - Neurocognitive

- **Multi-cancer early detection diagnostics through genetic testing and AI-driven imaging or blood tests**. These are both preventive and early-detection tests.

- **Hallmarks of aging assessment*** – The Hallmarks of Aging represent fundamental biochemical changes that occur universally across organisms undergoing biological aging, leading to a progressive loss of physiological integrity, impaired function, and, eventually, death [8]. Examples of such assessments are telomere length, DNA methylation, gut dysbiosis tests, as well as tests that measure mitochondrial function or inflammatory markers.

- **Biological age measurements** – These measurements are specific to the longevity field. Biological age markers will be discussed in detail in the next section.

    - Biological age measurements encompass a broad range of assessments that examine aging at multiple levels. Notably, organ-specific aging biomarkers can be used separately to assess the biological age and, hence, the general health of a specific organ. These assessments can be composite biomarkers when an algorithm calculates the age of an organ based on multiple measurements or biological age clocks based on DNA methylation.

* We have introduced a distinct category for Hallmarks of Aging, as some longevity clinics categorize their diagnostic packages under this heading, even though these assessments often overlap with other categories, such as biological phenotyping or biological age measurements.

Many of the diagnostic tools currently in use are new and the longevity medicine experts are still refining their understanding of how to interpret the results. Further research is needed to determine the clinical value of these tools and how to combine them to produce actionable insights. One notable study [9] was set to assess the value and clinical impact of surveying genome-wide disease-causing genes and variants. The study, conducted on a cohort of nearly 1,200 subjects from Human Longevity's San Diego clinic, was one of the largest and most comprehensive in which subjects were evaluated by precision prevention analytics. The participants underwent a range of assessments, including germline whole genome sequencing, whole-body MRI with quantitative imaging biomarkers, CT calcium scoring, cardiac ECHO, metabolomics, wearable monitoring, and extensive serum blood chemistries, among other tests.

The study found approximately one-in-six adults (17.3%) had at least one pathogenic genetic variant, which when integrated with deep phenotyping that included imaging, blood test and other analytical methods, one-in-nine (11.9%) had genotype and phenotype associations, supporting the clinical diagnosis of a genetic disorder.

Additional findings included:

- Insulin resistance and/or impaired glucose tolerance (34.2%)
- Elevated liver fat (29.2%)
- Cardiac structure or function abnormalities such as valvular disorders (16.2%)
- Significant calcified coronary artery plaque (calcium score > 100) (11.4%)
- Elevated liver iron (9.3%)
- Cardiac arrhythmias such as atrial fibrillation (6.1%)
- Cardiac conduction disorders (4.8%)
- Early stage tumors, most malignant (1.7%)

A lack of phenotype and genotype associations were observed in 5.8% of individuals with pathogenic genetic variants, further suggesting that the identification of pathogenic genetic variant(s) by sequencing alone is not sufficient for a definitive diagnosis, highlighting the importance of a multi-modal assessment.

The future of longevity diagnostics

Longevity diagnostics is on the cusp of a transformative era. It is moving towards more precise, multi-system assessments that provide an understanding of an individual's health up to a molecular level. The key to this future is AI, a technology that can analyze massive datasets and unlock new insights into our health. The following are the most anticipated solutions that are likely to revolutionize medicine in the next few years.

- Multiomics or phenomics is not just a new approach; it is a revolution in our understanding of health and well-being. By integrating data from diverse omic groups, including the genome, epigenome, transcriptome, proteome, metabolome and microbiome, we can analyze complex biological information and uncover novel associations. This comprehensive perspective will allow us to explore geno-pheno-envirotype relationships, transforming our understanding of disease and physiology.

- Personalized biological age assessments, customized to the individual's age or gender - Customizing clocks will allow for more precise assessments—for example, a young person's assessment should differ from that of an older individual.

- Deep immune phenotyping involves a global analysis of the relative cell distribution of blood cells, complete transcriptome or single-cell transcriptome and epigenome of white blood cells enabling a comprehensive characterization of cell type and state of differentiation. This method holds promise in predicting an individual's immune response to diseases and aiding in the identification of abnormal immune patterns.

- Deep phenotyping refers to a comprehensive analysis of disease traits or phenotypes that aims to understand diseases at a granular level by integrating various data sources and advanced technologies. Such deep phenotypic analysis will allow us to map the progression of the disease from wellness to disease state.

While the prospects for advanced healthy longevity medicine diagnostics appear promising, the incorporation of these tools is not without its challenges and concerns. To accelerate progress and increase accessibility, it is essential to address some of the following pressing issues:

- A pressing concern is that the precision diagnostics enabled by the innovative assessments may not lead to tangible outcomes but instead add to the overall cost. While precision diagnostics can generate vast amounts of data, the current lack of adequate tools for analyzing and interpreting this complex information may hinder our ability to identify effective interventions and treatments. Moreover, the shift towards at-home diagnostics will yield complex longitudinal data, further complicating the analysis. Therefore, it is crucial to develop a deeper understanding of potential therapeutics proactively to ensure that we are prepared to capitalize on the insights generated by these diagnostics. The use of artificial intelligence will be critical in identifying patterns, in deciding what changes are primary vs secondary (i.e. compensatory) changes. Longitudinal studies will also allow the identification of changes that are primary and pathogenic and could result in the identification of early therapeutic targets in each disease process.

- Another critical aspect of precision diagnostics is the risk of overdiagnosis. As we increasingly rely on advanced diagnostic tools, such as AI-driven MRI scans, which can be overly meticulous in detecting abnormalities, it is essential to mitigate the risks of overdiagnosis and false positives. Overdiagnosis can have significant implications, leading to unnecessary medical procedures and associated costs. For instance, a person flagged with a potential cancer risk may undergo extensive follow-up tests and diagnostics to confirm the initial assessment, resulting in unnecessary stress and financial burden. To minimize the likelihood of false positives and avoid unnecessary medical interventions, the field needs to establish robust protocols and guidelines for the interpretation of the results of innovative diagnostic assessments.

- Another critical challenge facing the field of healthy longevity medicine is the cost-effectiveness of the diagnostics. Currently, the high cost of longevity clinic services limits accessibility to non-affluent individuals, exacerbating the challenge of democratizing healthspan extension. However, some cost savings can be achieved by better understanding the tools, consequently providing individuals with precisely what they need and avoiding unnecessary assessments. While the cost issue remains a significant challenge, Dr. Roizen remains optimistic, foreseeing substantial advancements in diagnostics and therapeutics within the next 5 to 10 years that will be more cost-effective. Dr. Ezzat-Velinov highlights the potential shift of diagnostic tools from clinics to home settings, promising a substantial cost reduction. Furthermore, the development of AI-driven multi-assessment solutions, such as AI-driven scans, holds promise for more efficient and cost-effective diagnostics.

Biological aging biomarkers – what do they actually measure?

The most distinctive diagnostic tools in healthy longevity medicine are biological age clocks. A biological age clock functions as a tool to assess how quickly or slowly an individual is aging relative to their chronological age [10]. Effective biomarkers of aging must reflect the diverse biological processes underlying aging and its consequences while remaining sensitive to interventions targeting aging [11].

While efforts were made to create a universal biological age clock for the entire organism, initial attempts, like Steven Horvath's [12] DNA methylation-based clock, were based on population data and hence lacked the necessary accuracy in individuals due to influences from factors such as disease [11]. The concept of a universal clock becomes even more complex when considering that organs may age at different rates [13]. In light of the complexity and variability of aging, it may not be possible to establish a universal biological age clock. Furthermore, it appears that we still need to uncover what biological age clocks truly measure. The use of Mendelian Randomization (MR) will allow the establishment of causal relationships between molecular changes and disease and therefore increase the precision and efficacy of early therapeutic interventions.

Given the ongoing development of biological age measurement techniques, only a few clinics currently utilize biological age assessments to determine the biological age of various systems and gain a comprehensive understanding of a client's overall health and biological mechanisms, as measured by each specific clock. The longevity experts are still refining their understanding of biological age clocks and their correlation with health outcomes. To accommodate that problem, some clinics employ multiple biological age assessments to compare the results and identify potential areas for further testing. These assessments may include recently developed clocks that measure the aging rates of different organs or the recently developed intrinsic clock (Intrin Clock) that separates changes in immune subpopulations from aging of individual immune populations [11].

Dr. Eric Verdin from the Buck Institute suggests that, at present, the primary utility of these clocks lies in their ability to provide longitudinal insights into interventions. By employing one of these clocks, we can effectively track changes before and at different stages of intervention, offering invaluable data on the efficacy and impact of interventions over time.

Many clinics share similar views on the clocks as Dr. Verdin, and those who test their clients with biological age clocks do so before and after the interventions with the same set of aging biomarkers. Some medical centers also aggregate biological age data with other metrics, such as blood tests or wearable technology, to develop their in-house composite biomarkers. Companies developing their own composite biomarkers often collaborate with multiple test providers and longevity researchers, thereby advancing our understanding of biological age measurements.

Currently, there are many available biological age measurements. The most notable ones are as follows:

- **DNA methylation clocks** (Horvath, Levine etc.)
- **PhenoAge, GrimAge**: Correlations between DNA methylation and large data sets of common laboratory measures (glucose, CRP, albumin, etc.)
- **DunedinPACE**: DNA methylation correlated with the pace of aging
- **GlycanAge**: Composition of the IgG glycome
- **Aging.AI**: Deep transcriptomic and proteomic analysis
- **iAge**: Immunomics measures of inflammation
- And many more...

Source: [14]

Newer clocks:

- **IntrinClock** [11] —a clock developed by the Verdin lab at the Buck Institute. It was created by measuring the epigenetic age of distinct immune blood populations. It was discovered that existing clocks are measuring in part changes in the relative proportion of distinct immune cells in the blood. Naïve T cells were found to show an age 15-25 years younger than more differentiated T cells, such as memory T cells and terminally differentiated T cells (TEMRA). This would mean that a change in the relative proportion of these different immune populations, as observed after acute viral infection (i.e. COVID-19) would register as an increase in aging. A new clock was generated (IntrinClock) that eliminates this variable and measures intrinsic immune aging, regardless of immune activation. This clock is no longer sensitive to immune activation but still shows a unique increase during senescence.

- **OMICmAge** – a clock that incorporates the muli-omics approach developed by TruDiagnostics [15] and Harvard. Initial data shows that OMICm is 2-3x more predictive of age-related disease than other methylation clocks.

- **Liquid biopsies proteomics clocks enabling assessment of organ-specific aging** – Liquid biopsy proteomics clocks facilitate evaluation of organ-specific aging. These clocks are based on the analysis of proteins released by organs into the body fluids [16]. These are essential measures for diseases affecting specific organs, as accelerated aging of a particular organ has been linked to an increased risk of age-related diseases affecting that organ [13].

Another problem with the biomarkers of aging is the lack of standards and consensus on the properties of a reliable biomarker. That situation hinders their further development and validation for clinical applications. The Biomarkers of Aging Consortium [17] was established to address this issue - to define, validate, integrate into clinical practice, and ensure FDA approval for aging biomarkers.

One of the first achievements of the Consortium is a standardization of a definition of a biomarker of aging. According to the Consortium, „A biomarker of aging is a quantitative parameter of an organism that, either alone or in a composite, predicts biological age and, ideally, its changes in response to interventions. [14]

Experts from the Consortium hope that one of the new aging biomarkers will soon be accurate enough to be widely adopted and approved by official medical bodies. As soon as this happens, we will be able to evaluate longevity treatments and improve their effectiveness. The standardized biomarkers will bring the longevity field closer to being recognized as a credible branch of medicine.

Interventions used in longevity clinics

The absence of a validated biological age biomarker presents a challenge for the longevity field, hindering the ability to demonstrate and validate the effectiveness of longevity interventions to the broader medical community. This lack of standardization contributes to the wide variety of treatments offered among clinics and leaves room for interpretation and grey areas However, nearly all longevity clinics emphasize lifestyle optimization as the cornerstone of their approach. Dr. Kenneth Cooper, founder of Cooper Aerobics, highlights the importance of lifestyle, stating that *„The most under-appreciated risk factor for physical and mental health known to man is lifestyle. No drug can replicate the benefits of an active lifestyle."*

Research indicates that lifestyle changes can reverse the effects of many chronic diseases, including coronary heart disease [18], autoimmune diseases [19], or type two diabetes [20]. Longevity clinics leverage the latest technology and diagnostic tools to personalize and enhance their clients' lifestyle practices. They look at all aspects of health routines and optimize them if they find gaps.

As one of the cornerstones of good health, physical activity is prioritized in longevity clinics. In addition to motivating clients to achieve the minimum recommended 150 minutes of moderate exercise per week [21], many clinics personalize exercise plans based on factors like genomics, V_{O2} max measurement, physical assessments, and other specialized tests. Nutrition also receives significant attention, with personalized nutrition plans tailored to individual genetic profiles, food intolerances, and microbiome composition. Metabolic health assessments inform nutritional recommendations to address deficiencies, optimize metabolism, promote fat loss, and mitigate inflammation.

Sleep quality improvement is recognized as another crucial aspect of health optimization. Sleep impacts the regeneration of all human health systems, and its quality influences healthspan and longevity [22]. Longevity medical professionals put a lot of effort into analyzing their clients' sleep and applying appropriate interventions ranging from sleep coaching and breathing pattern correction to stabilizing glucose and reducing stress.

Stress management is another key focus area. Dr. Anna Erat from the Longevity Center pointed out, "We need stress, but in small amounts, to trigger an adaptive hermetic response, but

chronic high stress leads to deleterious effects and ultimately accelerates aging". Building stress resilience requires a multidimensional approach, and many clinics tackle this by offering bio- or neurofeedback, emotional regulation therapies, or teaching relaxation techniques or better breathing patterns.

Issues with stress response can also be caused by hormonal imbalances [23]. Longevity medical centers carefully assess hormonal health and try to correct it with lifestyle changes and nutrition. When these methods are insufficient or when the client's hormones are compromised due to aging, hormonal replacement therapy is offered. Interestingly, many conventional doctors offer hormonal replacement therapy, but what distinguishes longevity clinics' approach is ensuring that the doses and types of hormonal treatments are personalized. Clinics re-test the clients to ensure that such therapies are optimal.

When lifestyle improvements cannot be implemented due to clients' circumstances or limited motivation, longevity experts look for other solutions. Supplements are a popular option for busy clients who do not have the time, energy, or motivation to introduce changes to their health routines. However, very often, clients are more eager to take the supplements than the clinics willing to recommend them. Longevity supplements are still controversial due to limited data on their long-term effects or efficacy, and most of the evidence is derived from animal models. Longevity clinics hold very diverse viewpoints regarding supplements, reflecting varied philosophies. While some specialists advocate for their positive effects, viewing their potential preventive and protective actions as outweighing potential risks, others refrain from recommending them altogether. Some practitioners adopt a harm reduction approach, providing information on the best supplement options and possible risks to clients who express interest. Prof. Andrea Maier from Chi Longevity remarked, "We do not know if the supplements have antagonistic or agonistic profiles. Supplements need to be more regulated because they can potentially act as powerful geroprotectors". However, most supplements have no demonstrated efficacy and potential side effects that need to be further studied. The field of longevity can significantly accelerate the development of efficacious and safe supplements by rigorously testing their efficacy and safety in randomized clinical trials using the well-defined protocols established for approved drugs.

Longevity technology offers another avenue for enhancing health, with interventions like red and NIR light therapy, hyperbaric chambers, and cryotherapy proving increasingly popular. Hyperbaric chambers use high-pressure oxygen and are often utilized to support patients after stroke, improve muscle regeneration after intense workouts, and allow for super-compensation needed for muscle growth [24]. Cryotherapy – a therapy with very low temperatures is mainly used for inflammation reduction, improving blood circulation, and recovery after intense physical activity [25]. Phototherapy – treatment with various lengths of light affects the proper functioning of the entire body. Red and near-infrared (NIR) light plays a strategic role in many processes, including improving skin condition [26], reducing inflammation and pain, and accelerating body regeneration [27].

Finally, some clinics offer interventions that are still seen as costly or controversial. The controversies around the costs of these therapies or their efficacies are so significant that often, people associate longevity clinics with these therapies. Some associate longevity clinics with stem cell therapies or plasma exchange and are pretty surprised when they find out that most medical longevity clinics instead focus on prevention and lifestyle improvement. Nevertheless, some longevity clinics often try to reach a balance between available validated solutions and experimental therapeutics. Therefore, there is a solid need to regulate which interventions should be rigorously tested to further establish the validity of the whole field.

While regulations are essential, another crucial aspect of applying interventions is understanding the baseline for each client and then tracking the effect on each patient over time, a concept called “precision medicine”. Assessing the efficacy of longevity interventions in humans presents a significant challenge within the field. Given the complexity of human health and the multifaceted nature of interventions, pinpointing the precise impact of individual measures proves challenging. Consequently, there is a pressing need to develop more robust and systematic evaluation methods to gauge the effectiveness of interventions accurately.

Presently, most clinics employ aging biomarkers to evaluate the efficacy of their interventions, with biological age clocks being a popular choice. Additionally, clinics may utilize general health indicators like heart rate variability (HRV) and metabolic improvements evidenced by body fat and muscle mass changes on DXA scans. Moreover, subjective enhancements in well-being reported by clients during scheduled consultations throughout intervention programs also serve as a valuable assessment tool for many centers.

Moreover, it is expected that, in the future, AI will enable more specificity in proposing and evaluating interventions enabling designated personalized precision treatments for specific diagnostic issues. Additionally, once the biomarkers of aging are validated, efforts can be directed toward validating interventions aimed at reducing biological age. These interventions will be tailored to address specific aging-related needs.

What are the current activities of the field towards official recognition?

Validating a biomarker of aging and the efforts of the Biomarkers of Aging Consortium signify crucial steps toward garnering recognition from the medical community and regulatory agencies. In parallel, the longevity field strives for official approval by establishing a self-regulatory body known as The Healthy Longevity Medicine Society (HLMS) [28], initiated in August 2022. The HLMS spearheads various initiatives, including the formulation of guidelines, engagement with regulatory bodies like the FDA, and establishing a trial network for observational or clinical data. Governed by a geographically diverse Council, the HLMS is committed to fostering interdisciplinary collaboration and advancing education, research, and professional development in healthy longevity medicine, with the overarching goal of establishing it as a respected independent medical specialty that extends healthspan and optimizes individual performance.

Furthermore, education plays a pivotal role in legitimizing the field. A pioneering curriculum for physicians [29] was first established in 2019 by the Longevity Education Hub (longevity.degree) and launched on various platforms, i.e. NHS. Until today, it is the sole ACCME CME accredited free course for physicians, and it is entering the medical school core curricula in Q3 2024.

Additionally, two prominent academies are poised to become key players in educating medical longevity specialists: the Academy for Healthy Longevity [30], affiliated with the Yong Loo Lin School of Medicine at the National University of Singapore, and the forthcoming Longevity Academy under the Longevity Group's purview. These academies will offer a spectrum of courses and programs tailored to empower individuals with the necessary expertise to contribute to and lead in the domains of GeroScience and Healthy Longevity Medicine.

Collaboration and self-regulation are not just important; they are fundamental to establishing a robust and professional branch of medicine. Many longevity scientists have been advising numerous longevity clinics to ensure that their practices align with evidence-based approaches. Additionally, some clinics conduct their own research, sharing insights and findings with scientists and peers. Events like the Longevity Clinic Roundtable held at the Buck Institute will serve as platforms for experts from longevity medical centers to convene, exchange protocols, optimize methods, and begin laying the groundwork for policies and regulations. Given the field's nascent stage, collective diligence is crucial – a significantly toxic intervention could lead to adverse effects in patients and could harm the whole field and prevent further progress. Therefore, clinic representatives are eager to diligently research, define, standardize, and write guidelines for all the longevity concepts discussed above. The aim is to build a stronger brand among medical societies and propagate the longevity ideas within the public sphere.

How can healthy longevity medicine scale up and be more affordable?

Currently, longevity clinic services are predominantly restricted to more affluent individuals given their costs and the fact that their service are not recognized by existing reimbursement mechanisms, posing a significant obstacle to scaling up the healthspan extension at a lower cost. While AI holds promise for potentially reducing diagnostic costs and even intervention expenses, additional solutions must be explored.

One avenue for cost improvement lies in refining care models and tailoring treatments to individual needs. Central to this is embracing the „n=1" scenario, which underscores the importance of understanding each patient's unique profile. In traditional evidence-based medicine, diagnoses and treatments often rely on population models, presenting a challenge in establishing an individual patient baseline. However, the longevity field acknowledges that personalization is critical to extending healthspan. Factors such as biological mechanisms, lifestyle choices, and environmental influences vary greatly among individuals, influencing their response to interventions.

As we navigate a landscape of increasingly data-driven yet imprecise diagnoses, mitigating the risks of overdiagnosis and false positives becomes paramount, particularly with the emergence of new diagnostic tools like AI-driven MRI scans. Overdiagnosis can lead to unnecessary medical procedures and inflated costs. Robust protocols and guidelines for interpreting diagnostic results are essential to minimize false positives and prevent unnecessary interventions.

Finally, supportive communities are pivotal in fostering motivation and accountability among individuals striving for better health. Whether through online platforms or in-person groups, these communities facilitate friendly competition and mutual encouragement toward healthier lifestyles. Joanna Bensz, CEO of Longevity Center, underscores the importance of involving the entire family in adopting healthier habits, fostering a collective commitment to well-being.

The future of healthy longevity medicine

What lies ahead for the longevity field in the near future?

The concept of extending healthspan as a solution to the aging population challenge is gaining traction beyond the field itself. Notably, XPRIZE has introduced a healthspan category [31], offering a substantial $101 million prize for teams that can develop treatments capable of restoring muscle, cognitive, and immune function by a minimum of 10 years, with a goal of 20 years, in individuals aged 65-80 years within a treatment period of one year or less. This initiative aims to incentivize groundbreaking therapeutics targeting biological aging, potentially revolutionizing how we approach aging and bringing greater awareness to preventive measures, lifestyle changes, and healthy longevity medicine.

Beyond the XPRIZE and efforts to standardize practices, develop guidelines, validate biomarkers, and gain recognition from global medical agencies and regulatory bodies, there's a strong focus on enhancing the precision and cost-effectiveness of longevity treatments. Looking ahead over the next 5 to 10 years, advancements in diagnostics and therapeutics are expected to drive significant cost reductions. There's a possibility of diagnostic tools transitioning from clinics to home settings, making testing more accessible and affordable. With the increasing adoption of home tests and wearables, AI will play a pivotal role in analyzing data to provide personalized recommendations and improve therapy adherence through tailored coaching.

Moreover, we anticipate a reduction in the number of assessments needed to evaluate physiological health. Our organs release valuable analytes into the bloodstream, which can be captured through blood samples. AI can integrate these phenomics measurements with health outcomes and trajectories, streamlining the diagnostic process. Innovations like AI-driven MRI scans can offer comprehensive imaging assessments, simplifying what previously required multiple assessments. As AI evolves, these assessments will likely become more precise, reducing the risk of false positives and minimizing the need for additional evaluations to improve health. Additionally, AI-driven pharmacology and drug development show promise for personalized

interventions aimed at improving general health, preventing diseases, or extending healthspan. Overall, these advancements aim to advance precision personalized healthcare by integrating personal omics information (including genomics, transcriptomics, proteomics, metabolomics, and phenomics) with longitudinal data from real-time physiological monitoring devices.

Dr. Leroy Hood, CEO of Phenome Health, envisions that data-driven health will revolutionize prevention, noting, *"Thanks to biomarkers, in 10-15 years, we can get rid of 40% of major diseases"*. Moreover, leveraging a data-driven approach can effectively improve our options for reducing biological age and extending healthspan. With data-driven health solutions, we can effectively map the three stages of health: wellness, disease, and the transitions between them. The ability to detect disease at these pivotal transition states will transform clinical practice. The longevity field's aspiration is that this innovative healthcare model will allow broader access to improved health for all while significantly reducing personal and public healthcare expenditures.

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