Longevity Biomarkers Landscape Overview

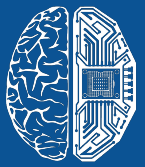
Teaser

Q4 2021

October 2021

LONGEVITY.INTERNATIONAL

Aging Analytics Agency



Deep Knowledge Group

www.longevity.international

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The growing geriatric population and **increasing prevalence of chronic diseases** are the key factors projected to boost the **diagnostic market growth** over the forecast period. Our report is focused on the diagnostic of aging that include **direct evaluation of biological age** and **prediction** and **prognosis age-related disorders**. The paper provides a thorough list of single biomarkers and biomarker panels of biological age, together with extensive and enhanced profiles. It explores their advantages, disadvantages, future perspectives, challenges and opportunities, with a focus on technologies currently used for assessment.

Biomarkers are an essential factor in the **Aging Analytics Agency's** strategic agenda, which includes policy proposals to national and international governance bodies on how to **effectively increase National Healthy Longevity** via practical implementation of **P4 medicine technologies**. It is essential to develop and promote the widespread use of panels of biomarkers that are validated and actionable.

Here we also have highlighted the increasingly necessary role of **AI technology** that will play in coordinating the practical implementation of Longevity biomarkers due to the sheer volume of life and health data involved. We believe that the application of AI for Longevity will **bring the greatest real-world benefits** to the industrialization of Longevity to scale, and that will serve as the **main driver of progress** in the widespread extension of healthy Longevity for all segments of society in the coming years.

Approach of the Report

Database

300	495	235
Companies	Investors	R&D Centers

The database was formed based on:

- the **identification of companies and R&D centers** that develop or implement Biomarkers of Aging and age-related diseases;
- the **determination of investors** that contributed money to these companies.

Applied Research and Analytics Methods

Descriptive Analysis	Mixed Data Research	Data Triangulation
Comparative Analysis	Qualitative Data Collection	Data Filtering

Data Sources

Media Overview (Articles and Press Releases)	Industry-Specialised Databases	Publicly Available Sources (Websites)	Industry Reports and Reviews

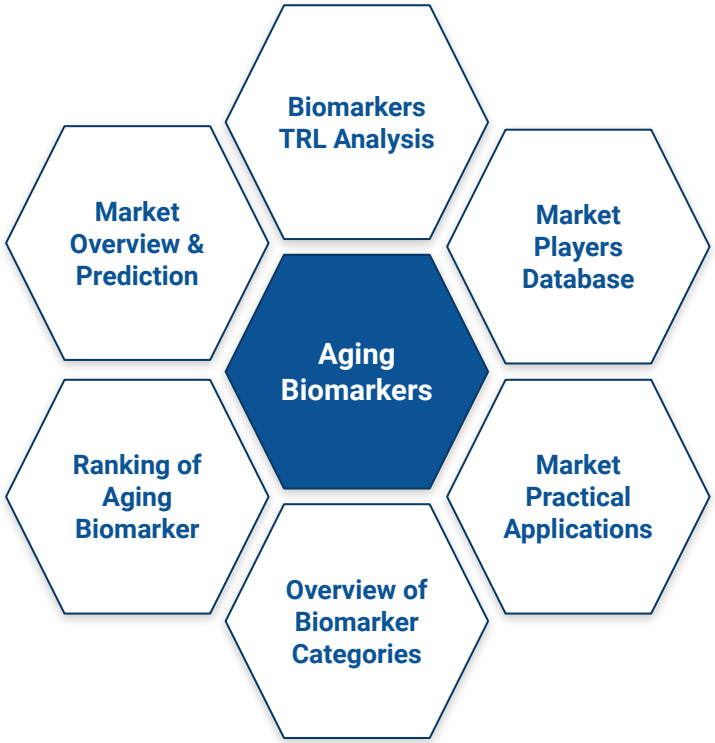
Relying on various research methods and analytics techniques, the analytical provides a comprehensive overview of the Longevity Biomarkers Landscape. This approach has certain limitations, especially when using publicly available data sources and conducting secondary research. Aging Analytics Agency is not responsible for the quality of the secondary data presented herein; however, we do our best to eliminate the said risks using different analytics techniques and cross-checking data. Please note that we did not deliberately exclude certain companies from our analysis, nor was it due to the data-filtering method used or difficulties encountered. The main reason for their non-inclusion was incomplete or missing information in the available sources.

Executive Summary

Aging is a physiological accumulation of functional losses during life, underlined by changes in the molecular mechanisms of the body functioning. The chronological age of the organism does not always indicate well the functional state of the organism. People of the same age can have different levels of health and abilities, as well as different rates of aging. **Biomarkers of Aging** are the key tools for assessing the wide range of physiological processes that underlying aging and the appearance of age-related diseases.

This analytical case study includes an unexampled database that provides a closer look at the companies, clinics, investors, R&D centers leading by the specific mechanisms of aging involved. Key players of this industry are reviewed and analyzed precisely. Market meta-analysis offers a unique view of market patterns and future prospects. The categorization and evaluation of businesses provide information into the distribution of future pressures. Each category of Aging Biomarker is examined separately. Furthermore, in-depth research analyzes provide an overview of product trends and treatment strategy dynamics.

Main Features of the Analytical Case Study



Executive Summary

This report is an overview version of research study on the **longevity biomarkers** aiming to provide :

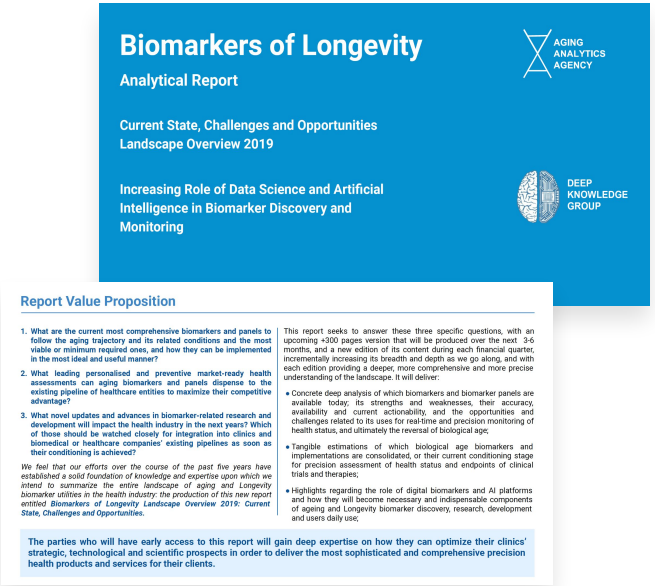
- Concrete deep analysis of which **biomarkers and biomarker panels** are available today; their strengths and weaknesses, accuracy, availability and current actionability, their strength, and weaknesses, and peculiarities of each type of longevity biomarkers related to its uses for real-time and precision monitoring of health status, and biological age;
- Tangible estimations of which **biological age biomarkers** and implementations are consolidated, or their current conditioning stage for precision assessment of health status and endpoints of clinical trials and therapies, the use in insurance risk assessments;
- Highlights regarding the role of **digital biomarkers, digital avatars and AI platforms** and how they will become necessary and indispensable components of aging and Longevity biomarker discovery, research, development and users daily use; overview of mobile apps containing actionable biomarkers or aging clocks.

1. **Existing biomarkers/biomarker panels,** their availability and current actionability.
2. **Application of biomarkers** to longevity, aging, aging clocks and age-related diseases.
3. **Biomarkers' accuracy**, their **strengths**, **weaknesses**, **threats**, and **opportunities**.
4. The increasing role of **digital biomarkers,** especially **digital avatars.**
5. The **importance of AI** in the biomarkers' discovery, validation and implementation.
6. The **implementation of longevity biomarkers in finances** and insurance risk assessments.

Introduction

In 2019, Aging Analytics Agency produced **Biomarkers of Longevity Landscape Overview 2019**, an open-access special analytical case study that uses comprehensive analytical frameworks to rank and benchmark existing panels of biomarkers of aging and longevity according to their ratios of accuracy vs. actionability, identifying the panels of biomarkers that can have the greatest impact on increasing both individual and national healthy longevity in the next few years, for use by a wide variety of strategic decision makers including companies, investors, governments and insurance companies.

The report was designed to make **key strategic recommendations regarding technologies and biomarkers implementations** within the reach of companies, entities and nations in order to assist them in optimizing their developmental plans and strategies, providing **specialized guidance for business and investment core decisions**, including a comprehensive list of single biomarkers of aging and panels (their advantages and disadvantages), a concrete analysis of recent novel biomarkers of aging, **an overview of AI platforms** as a necessary and indispensable components of longevity biomarker discovery.



Source: Biomarkers of Longevity Landscape Overview 2019

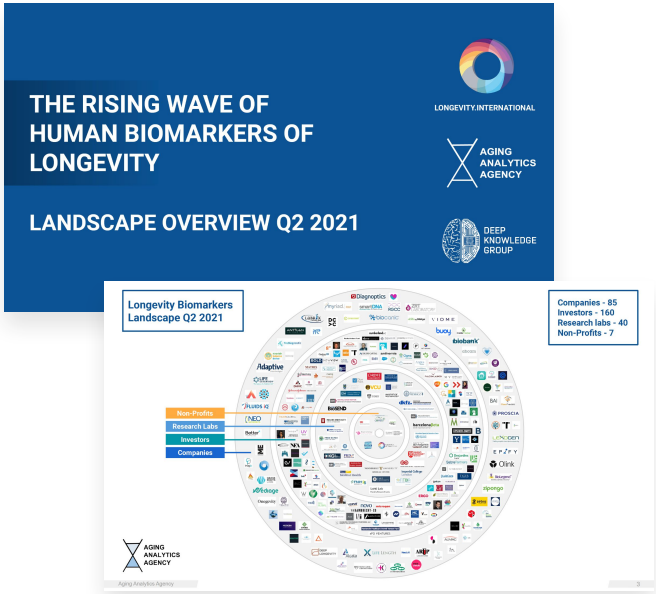
Introduction

The next edition of the **Longevity Biomarker Ecosystem Q2 2021** report was published in May 2021, providing an enhanced overview of 85 companies, 160 investors, and 100 biomarker panels.

Deep Knowledge Group considers longevity biomarkers as a strategic core engine for its longevity activities and as a major catalyst for the development of the whole longevity industry. They represent the major key to transforming aging science theory into practical Human Longevity applications over the next several years. Moreover, biomarker panels can be used as tangible, validated tools to evaluate, benchmark, and compare longevity companies, conducting data-driven evidence-based due diligence.

Therefore, the question of access to the top expertise in longevity biomarkers is of a strategic importance for Deep Knowledge Group.

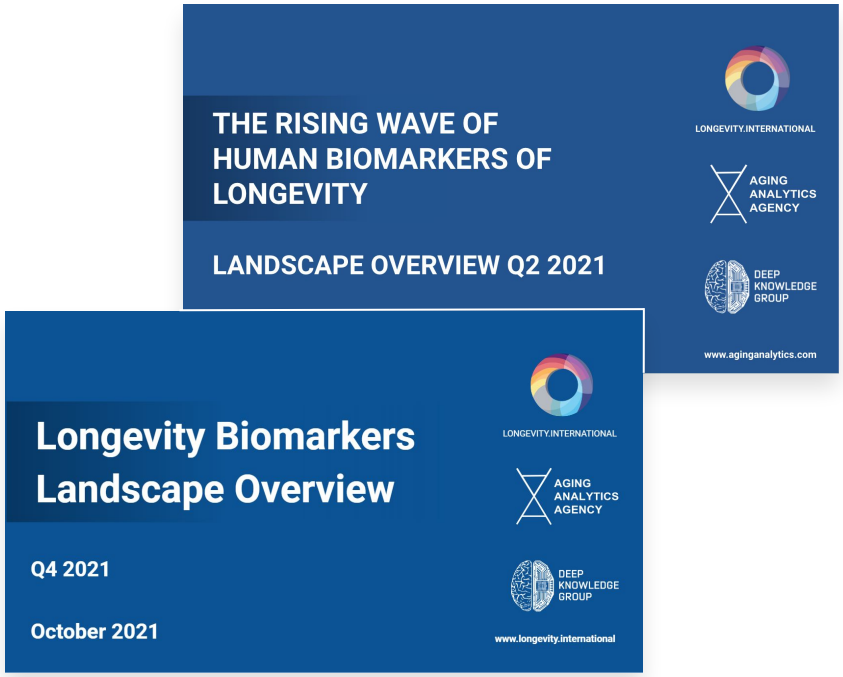
Further, longevity biomarker panels can be applied for financial products structuring, namely InsurTech and more complex financial products later on (such as for example HALE/QALE derivatives, biological age financial options and futures, and so on).



Introduction

Longevity Biomarkers Landscape Q4 is a special analytical case study by Aging Analytics Agency which is an updated version of The Rising Wave of Human Biomarkers of Longevity: Landscape Overview 2021 and provides a comprehensive overview of the Longevity Biomarkers Landscape, which is rapidly developing.

The report includes a **more detailed description of biomarker varieties**, **updated biomarkers classification**, **a timeline of their development**, and **updated private and public sector biomarker adoption guidelines** to help them find the tools they need to optimize their strategies and action plans, as well as specialized guidance for business, investment, and policymaking. Demonstrates professional potential to provide a **fundamental understanding of the significant challenges and opportunities** being faced in this area, or how they can be used to maximize benefit and to avoid potential pitfalls by individuals, institutions, and even entire governments.

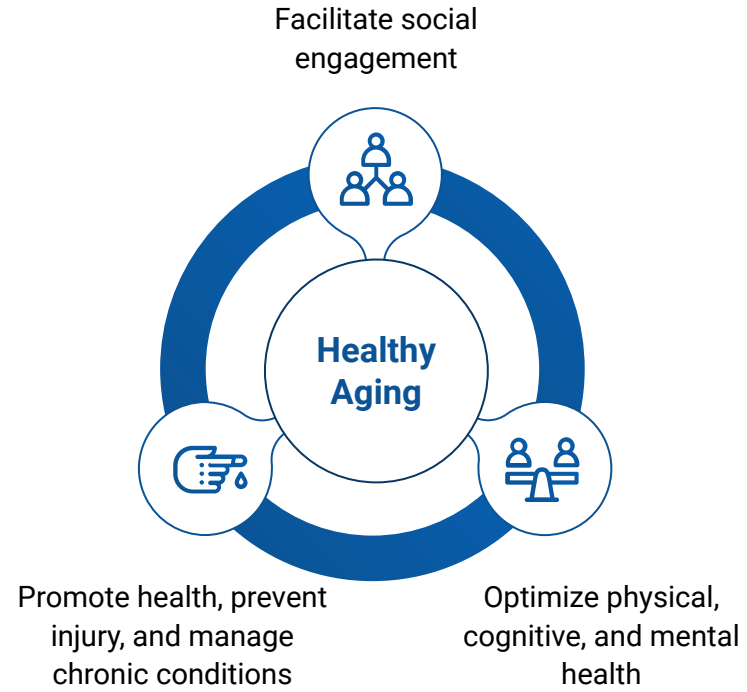


Concept of Aging

Aging is a global phenomenon that began some 3.5 billion years ago with the genesis of life. The accumulation of the many changes caused by aging in cells and tissues alter it's function and can finally lead to death. Genetic abnormalities, the environmental factors, illnesses — all of those contribute to aging changes. **9 hallmarks of aging** (listed on the next slide) that were defined to characterize aging process on the cellular level.

Under optimal living conditions, the degree of accumulation of aging changes limits average life expectancy at birth to about 85 years and maximum life span to around 122 years. Due to incremental improvements in living circumstances, such as diet, housing, and medical care, these limitations have been slowly increased over the previous 2000 years. As such, life expectancy in ancient Rome was about 30 years, while reaching to almost 80 years today in the developed countries.

In today's society, healthy aging and well-being are widespread public and governmental objectives. The recognition that much of the cost of health and social care in economically developed countries is consolidated in the last decade or two, as well as the major demographic shift towards higher proportions of older adults in the population in many countries around the world, have sharpened the research focus on aging.



Source: Harman D. Aging: Overview

The Hallmarks of Aging

Genomic Instability

Aging can be the consequence of increased DNA damage accumulation. This is due to physical, chemical, and biological agents, as well as DNA replication errors, spontaneous hydrolytic reactions, and reactive oxygen species (ROS).

Telomere Attrition

Telomeres are the chromosomal regions located on the ends of chromosomes. They tend to become increasingly shorter after each DNA replication. When this sequence ends, the cell dies. Telomerase deficiency in humans is associated with age-related diseases.

Epigenetic Alteration

Epigenetic changes involve alterations in DNA methylation, post-translational modification of histones, and chromatin remodeling. It can lead to abnormal function of cell.

Loss of Proteostasis

Proteostasis involves mechanisms for the stabilization of correctly folded proteins, as well as mechanisms for the degradation of abnormal proteins. These processes tend to change during aging.

Deregulated Nutrient Sensing

Nutrient sensing includes trophic and bioenergetic pathways, such as insulin and IGF-1, signaling pathways, and other systems (mTOR, AMPK, and sirtuins).

Mitochondrial Dysfunction

There is a noticeable reduction in ATP generation and increased electron leakage in the respiratory chain caused by aging. It is associated with mitochondrial damage.

Cellular Senescence

Cellular senescence can be defined as a stable arrest of the cell cycle. The accumulation of senescent cells in aged tissues can lead to age-related disease progression.

Stem Cell Exhaustion

Stem cells are cells from which all other cells with specialized functions are generated. There is a substantial decrease in the number of stem cells during life. Recent studies suggest that stem cell rejuvenation may reverse the aging phenotype.

Altered Intercellular Communication

Neurohormonal signaling tends to be deregulated in aging as inflammatory reactions increase, while immunosurveillance against pathogens and premalignant cells declines.

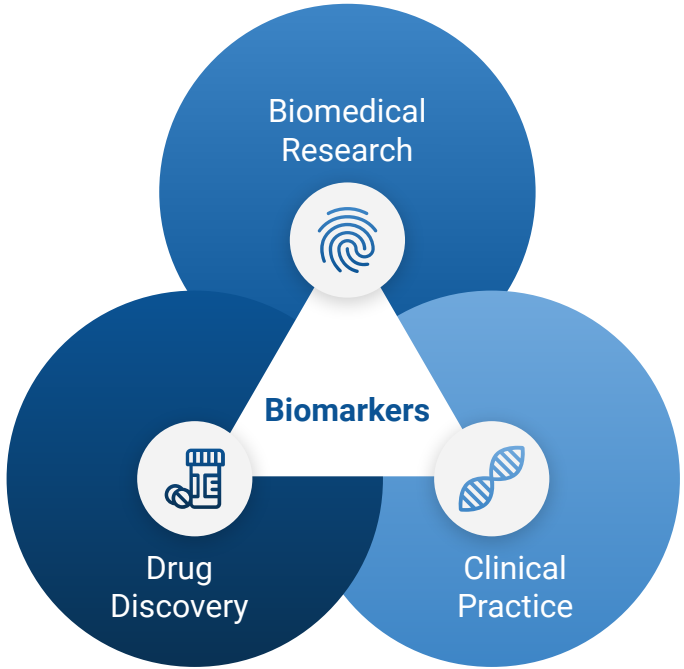
Source: López-Otín, Carlos et al. “The hallmarks of aging.”

Concept of Biomarkers

A **biomarker** or a **biological marker** is a characteristic that is objectively measured and evaluated as an indicator of some biological state, condition or process. Biomarkers are used in many scientific fields and commercial activities, and subjected to several and dissimilar classifications that follow different criteria.

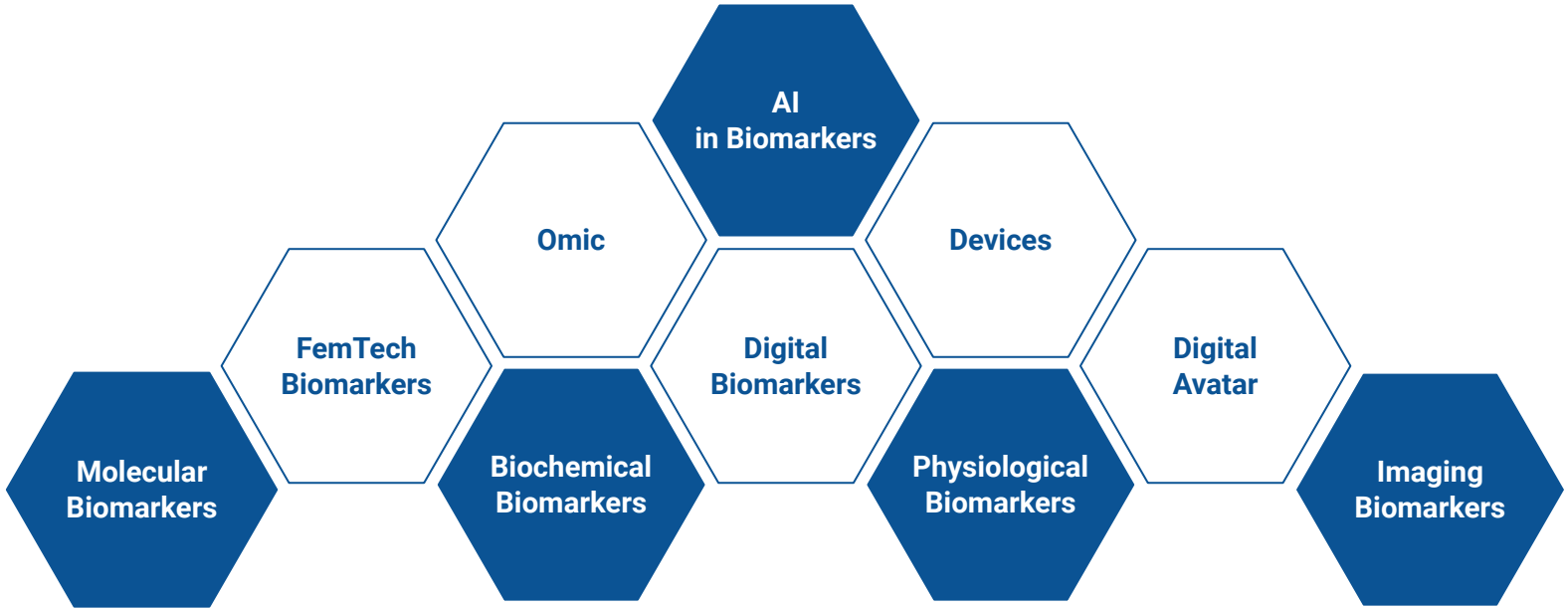
In **biomedical research** and **clinical practice**, biomarkers include measurements that suggest the etiology of, susceptibility to, activity of, or progress of a disease. The use of biomarkers in basic and clinical research as well as in clinical practice has become so commonplace that their presence as primary endpoints in clinical trials is now accepted almost without question.

In **drug discovery and development**, biomarkers can be used to predict or identify safety problems related to a drug candidate, for patient selection for clinical study enrollment, stratification of patients during study, identification of toxic responses before they become clinically evident, in addition to reveal an expected or unexpected pharmacological activity such as reversal, deceleration or acceleration of biological age, the particular case that appeals us.



Longevity Biomarkers Framework

Ahead of database creation, we picked the **most significant types of biomarkers of aging**. The categorization of companies is based on the source of biomarkers, their focus level, practical outlook, and methodology. The framework not only brings a **comprehensive view of the market,** but also **sustains relevance in advance to the development** of technologies and research approaches.



Longevity Biomarkers Landscape Q4 2021

AI Biomarkers

Companies - 300
Investors - 495
R&D Centers - 235
Non-Profits - 7

Digital Biomarkers

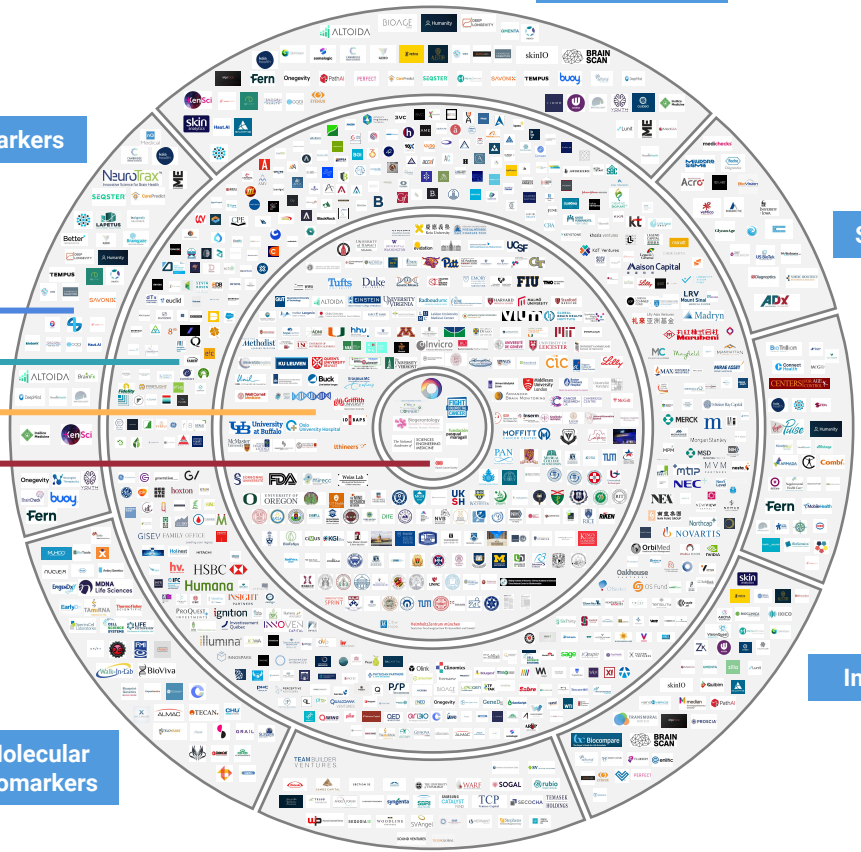
Systemic Biomarkers

Companies

Investors

R&D Centers

Non-Profits



Physiological Biomarkers

Imaging Biomarkers

Molecular Biomarkers

Omic-based Biomarkers

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Classification of Biomarkers of Aging

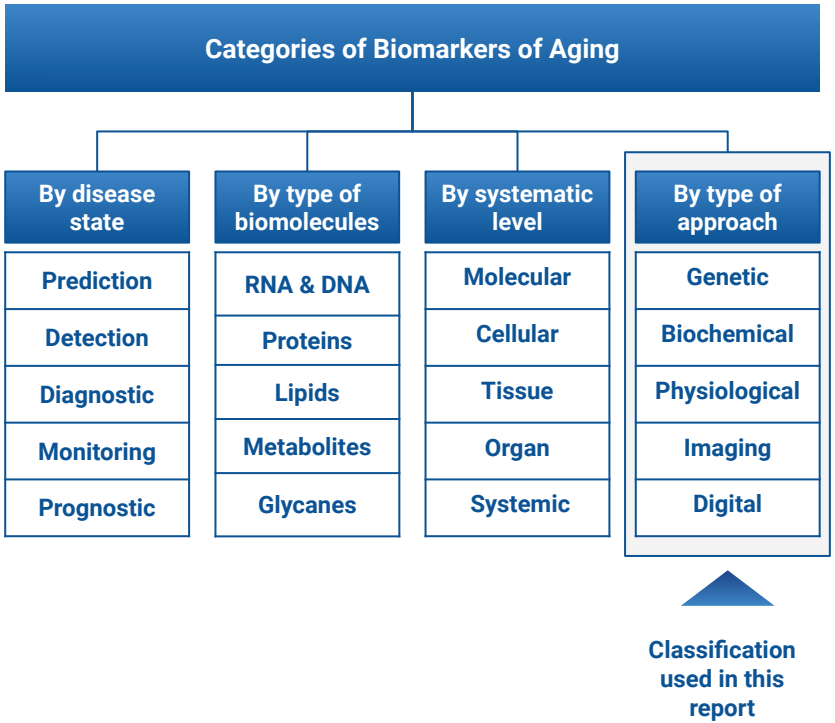
In older adults, chronological age may not be the best predictor of **residual lifespan** and **mortality**, because with age the heterogeneity in health is increasing. **Biomarkers for biological age** and **residual lifespan** are being developed to predict disease and mortality better at an individual level than chronological age.

Classification of Biomarkers of Aging can be based on different parameters, including their characteristics, such as age-related disease state, type of biomolecule, systematic level of diagnostics or type of diagnostic approach.

In our report we have used classification **by diagnostic approach** which includes:

- **Genetic and Biochemical** biomarkers that describe changes on molecular level (mutations or polymorphisms and quantitative gene expression analysis, peptides, proteins, lipids metabolites, and other small molecules in biosamples),
- **Physiological** biomarkers show functional changes of organs,
- **Imaging** biomarkers (computed tomography, positron emission tomography, magnetic resonance imaging) show morphological changes in tissues and organs.
- **Digital** biomarkers are defined as objective, quantifiable physiological and behavioral data that are collected and measured by means of digital devices such as portables, wearables, implantables, or digestibles.

Age-Related Biomarkers Classification



Source: Britannica-aging, Proteomics and System Biology

Development of Biomarkers of Aging

For the last two decade years, the **increasing prevalence of chronic diseases**, advancements in the **techniques** used for the development of biomarker-based diagnostics, and the **growing geriatric population** are factors likely to **boost the biomarkers market** significantly throughout the forecast period.

A new wave of scientific and commercial interest to Biomarkers of Aging **brings original solutions** for evaluation of biological age. The main mechanisms identified as potential biomarkers of aging are DNA methylation, loss of histones, and histone modification. The uses for biomarkers of aging are ubiquitous and identifying a physical parameter of biological aging would allow humans to **determine our true age**, **mortality**, and **morbidity**. The change in the physical biomarker should be proportional to the change in the age of the species. Thus, after establishing a biomarker of aging, humans would be able to dive into research on **extending life spans** and finding timelines for the arisen **of potential genetic diseases**.

Challenges to Develop of Informative Biomarkers for Longevity and Aging

- the **biological variation** between individuals that makes generalizations difficult;
- the **overlapping of aging and disease** processes;
- uncertainty **regarding benign** versus **pathogenic age-related changes**;
- the point at which a process **begins to do damage** to the organism, and, if so, when does it occur;
- when to distinguish **critical damage** from **non-critical**;
- difficult to obtain **funding** for this research.

Source: Butler RN. et al. Biomarkers of aging: from primitive organisms to humans. J. Gerontol

Evaluation of Biomarkers of Aging

Systemic Approach for Aging Rate Assessment

Biomarkers of Aging (AFAR* Criteria)

- Predict the rate of aging;
- Monitor a basic process that underlies the aging process, not the effects of disease;
- Must be able to be tested repeatedly without harming the person;
- Work in humans and in laboratory animals

Biomarkers of Age-related diseases

- Minimally invasive
- Routinely used for Clinical Diagnostics
- Comprehensive
- Reliable

Despite the growing interest to **Aging evaluation** there is still **no gold standard** of reliable biomarkers to predict and monitor Aging rate. Aging is a time-dependent multisystemic functional decline and it is evaluated at different levels: molecular, systemic, physiological.

Several attempts to establish markers of aging have been made over the last 50 years, but the complexity of the aging phenotype poses both **conceptual and practical challenges**.

Despite previous efforts, there is presently **no commonly accepted definition ofBiomarkers of Aging** or either criterias for their selection, resulting in an **absence of reliable, verified methods** for measuring healthy aging.

Biomarkers of healthy aging might be used as surrogate endpoints or outcome measures in trials of treatments aimed at extending life expectancy, and accurate, easily-measured indices of healthy aging could be used in public health-related population surveys.

However, there is **no standard reference for measuring healthy aging**, which makes conducting and assessing aging research across studies problematic.

**AFAR - American Federation for Aging Research*

Source: Lara, Jose et al. “A proposed panel of biomarkers of healthy aging.” BMC medicine

Practical Application of Age-Related Biomarkers

01 Clinical Trials

- New pathways identification
- Age-adjusted clinical trial enrollment

02 Reproductive Longevity

- Reproductive longevity tracking
- Family-planning timelines

03 Preventive medicine

- Feature transfer from aging to disease
- Age-related disease screening and staging
- Immunosenescence analysis

04 Treatment & Diagnostics

- Age-personalized immuno-oncology treatment
- Mortality prediction
- Age-personalized vaccines

05 Healthy Living

- Wellness
- Sport
- Nutrition
- Life insurance

Report Methodology

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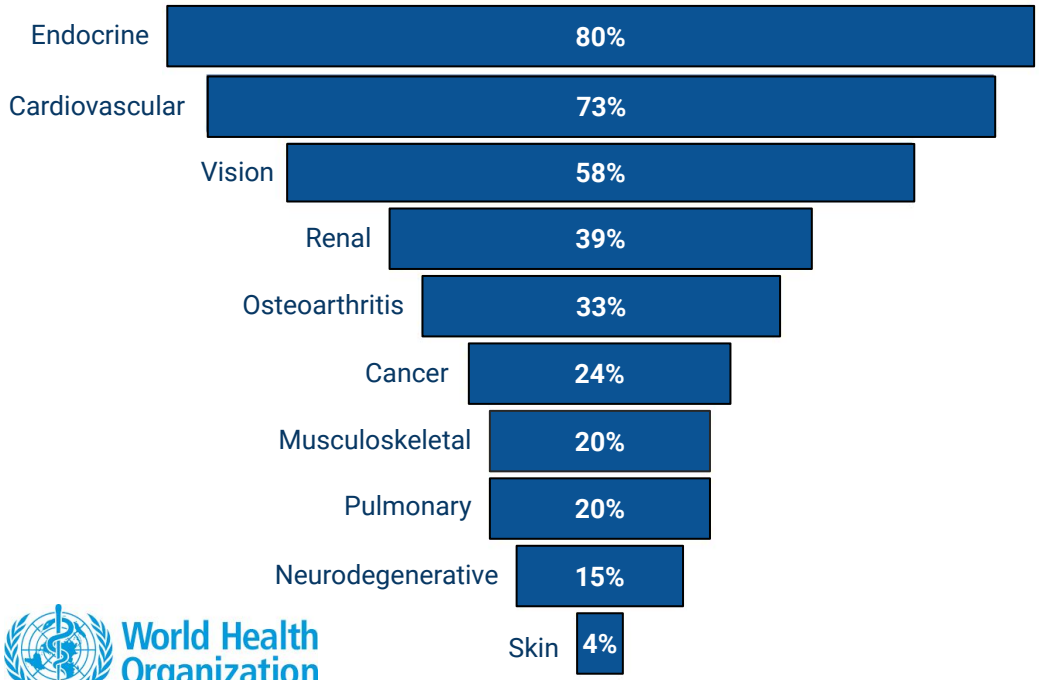
Biomarkers Selection by Prevalence of Age-Related Disorders

Prevalence of Disorders in Patient Group in Age >60, %



World Health Organization

The world's **population is aging rapidly**. Between 2015 and 2050, the proportion of the world's older adults is estimated to almost double, from about 12% to 22%. In absolute terms, this is an **expected increase** from 900 million **to 2 billion people** over the age of 60. older adults face special health challenges which need to be recognized.

Multiple studies shown dramatical statistics in older cohort of patients. Approximately 80% of people develop endocrine disorders (33% of them have diabetes), 73% - cardiovascular disease (24% have coronary heart disease), 58% have problem with eyes and vision (18% seniors have amblyopia).

According to this prevalence of age-related disorders, we have selected biomarkers for our analysis.

Biomarkers Classification

Classification by Diagnostic Approach

Molecular	Biochemical	Physiological	Imaging	Digital
• Genetic • Epigenetic • Non-Epigenomic	• Senescence • Metabolic • Inflammatory • Mitochondrial • Cell architecture	• Functional • Morphological • Behavioral • Cognitive / mental • Stress etc.	• Radiological • MRI *(Magnetic resonance imaging)* • PET *(Positron emission tomography)* • Optical	• Smart devices • Neurocognitive biomarkers

Artificial Intelligence and Biomarkers

Omic Biomarkers | **Digital Avatar** | **FemTech Biomarkers**

For this report, we used biomarker **Classification by Diagnostic Approach** because this classification covers the **largest spectre of biomarkers** and **modern approaches for diagnostics**. As a separate **sub-categories** we have selected **Omic biomarker, Digital Avatar, FemTech Biomarker** based on combination of traditional diagnostic approaches and **AI / Machine Learning**. However, this classification is not final and can be changed in the next versions of the report.

Concept of TRL

In the report we applied several evaluation metrics — qualitative and quantitative — to assess accuracy, availability, actionability and ethical aspects of single biomarkers or panels of biomarkers. Those included Accuracy Index, Availability Index, Actionability Index, Publication Index — all explained further.

For different types of aging clocks, in the suggested categorization framework, we estimated combined Technology Readiness Level (TRL) using a standard industry classification metric developed by NASA and measuring any technological solution from 1 to 10 — former being a stage of technological research, and 10 being a commercially available solution. We have identified TRL for select single biomarkers in each aging clock category and than applied an average for a category as a whole.

For each type of aging clocks we also conducted Strength, Weaknesses, Opportunities, and Threats (SWOT) analysis based on our qualitative expert assessment criterias.

Finally, for the purpose of understanding ethical and legal risks involved in the application of advanced longevity biomarkers in certain consumer-oriented non-medical industries, like the insurance industry, we have made a qualitative risk assessment study and applied Ethical Risk Assessment Index — from 1 to 5 — 1 representing low risk and 5 representing the highest risk.

Technology Readiness Level (TRL) gradation principle:

TRL 10	Proven Operations
TRL 9	System Operational
TRL 8	Subsystem Build and Test
TRL 7	Detailed Design and Prototype Validation
TRL 6	Preliminary Design and Prototype Demonstration
TRL 5	Conceptual Design and Prototype Demonstration
TRL 4	Technology Demonstration
TRL 3	Proof-of-Concept
TRL 2	Technology Concept
TRL 1	Technology Research

Source: Straub. In search of technology readiness level (TRL) 10. 2015.

Molecular Biomarkers

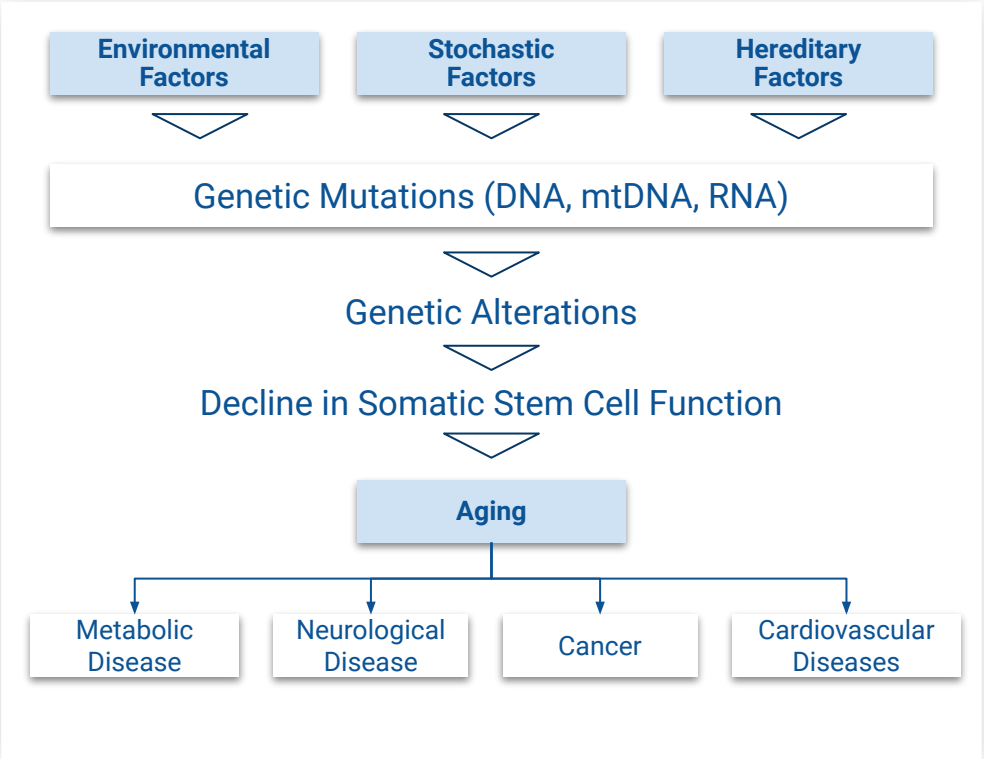
Category Characterization

The **environmental conditions** (stress, pesticides), **individual genotype** (genomic and mitochondrial DNA) and **stochastic factors** can induce **genetic and epigenetic alterations** that cause a decline in somatic stem cell function that can be the origin of metabolic, degenerative diseases, cancer and aging in the individuals.

In our report we have **analysed companies** which **offer Molecular Biomarkers for aging and age-related disease** that are clinically approved and have significant scientific evidence.

We include in our analysis **genes associated with age-related disease** as Endocrine disorders (Diabetes, hypothyroidism), Cardiovascular disorders (stroke, heart failure etc),Vision disorders (glaucoma, cataract), neurodegenerative (Alzheimer's, Parkinson, Sclerosis) etc. as well as **genes and mutations responsible for progeroid syndromes** (age-related monogenic hereditary disorders) and **populations of centenarians** whose lifespan is approximately twice the mean predicted for the population at the time of their birth will help to establish the function of a specific genotype in an individual's lifespan.

Genetic Factors' Influence in Aging and Lifespan



Molecular Biomarkers Framework

By Research Field

Genetic

- Genetic Mutations (DNA, mtDNA, RNA)
- SNP Genotyping

Epigenetic

- DNA Methylation
- Telomere Length

Non-Epigenetic

- Shelterin Complex
- Telomere Length

Molecular Biomarker market has been segmented by the approach in Genetic and Epigenetic diagnostic of **aging and age-related disease**. Also this market has been segmented by their **end-user of product**:

- accredited clinical laboratories,
- at-home tests,
- biotech companies (developing new biomarkers),
- service.

The growth amongst these segments will help you analyse meagre growth segments in the industries, and provide the users with **valuable market overview** and **market insights** to help them in **making strategic decisions** for identification of core market applications.
The most informative and **reliable genes** and their **mutations** associated with Aging has been proposed.

Key Companies: Molecular Biomarkers

Genetic

Genetic Mutations

DNA

ALMAC · GRAIL · RGCC · MAYO CLINIC LABORATORIES · Blueprint Genetics · Radboudumc · CHU de Poitiers Télémédecine · CBI Toulouse Centre de Biologie Intégrative · Assistance Publique Hôpitaux de Paris · HUG Hôpitaux Universitaires Genève · IMOMA · CHUV · St.Mary's General Hospital · Universität Zürich

mtDNA

BAYLOR GENETICS · Ambry Genetics A Konica Minolta Company · athena diagnostics · NHS East London NHS Foundation Trust · MDNA Life Sciences · VCGS Leaders in Genetic Health · CENTOGENE The Rare Disease Company

RNA

ALMAC · TAmiRNA stability for life. · HUG Hôpitaux Universitaires Genève · MAYO CLINIC LABORATORIES

SNP Genotyping

CD Genomics The Genomics Services Company · Assistance Publique Hôpitaux de Paris · CHUV · CBI Toulouse Centre de Biologie Intégrative · Radboudumc · MAYO CLINIC LABORATORIES · XVIVO BIOSCIENCES · RGCC · SALIMETRICS

Epigenetic

DNA Methylation

genknowme Personalized prevention solutions · MUHDO YOUR HEALTH MATTERS · St.Mary's General Hospital · ACTIVE MOTIF · adela · MDxHealth · RGCC · VitaLife MD Add Vitality to Your Life · Inherent Biosciences · AGELESSLX · TECAN · BioViva · TWIST BIOSCIENCE · ELYSIUM · LIFE EXTENSION · GRAIL · ZYMO RESEARCH · Capsulomics · Chronomics · NUCLEIX · MODERN WELLNESS DIAGNOSTIC SERVICES · CC DIAGNOSTICS · EarlyDx · MAYO CLINIC LABORATORIES · EPIGENDX · myDNAge · FOXO · Extended Longevity · US-EPI · EPIFY · FMI Friedrich Miescher Institute for Biomedical Research

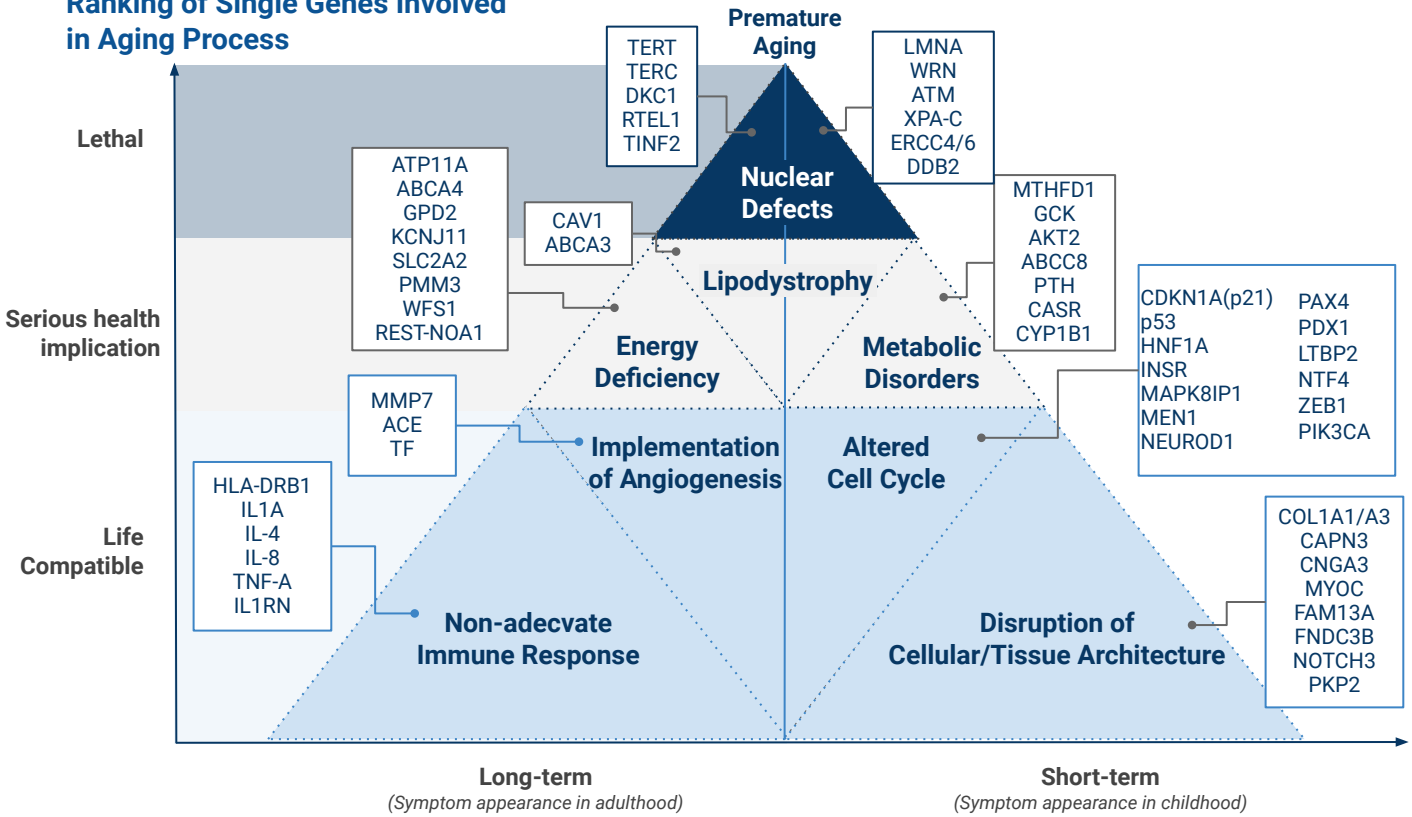
Non-Epigenetic

Telomere Length

BioTools Innovative Tools for Life Sciences · Cell Science Systems · TELOYEARS Know how well you're aging. · ThermoFisher SCIENTIFIC · Dako · ScienCell Research Laboratories · Roche · TELOMERE DIAGNOSTICS · Extended Longevity · kpbs · LIFE LENGTH · SpectraCell Laboratories Science + Health + Solutions · SelfDecode · Istituto Giannina Gaslini

Aging Genetics and Aging

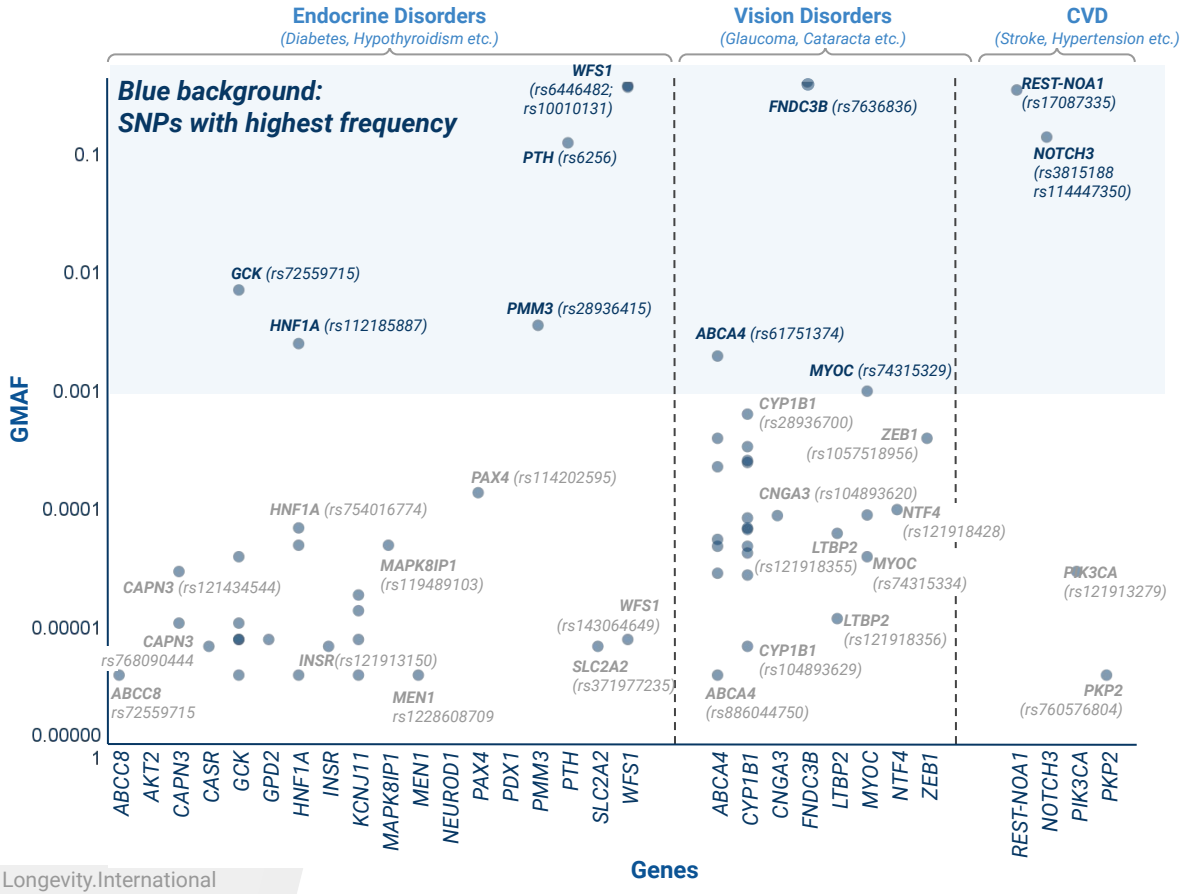
Ranking of Single Genes Involved in Aging Process



We have **analysed the published genetic studies** for two different populations: **1. centenarians** whose lifespan is approximately twice the mean predicted for the population at the time of their birth; **2. patients with extremely accelerated aging** as progeria, Werner syndrome etc. These data has helped us to **select the certain genetic factors** which act as modulators of the aging process. Presented **genes are associated with lifespan, resistance to diseases** that lead to early death.

In families whose members show **exceptional longevity,** in addition to other **environmental factors**, **family habits** (lifestyle, nutrition) are thought to influence survival, although data are limited on the contribution of these factors to greater resistance to disease.

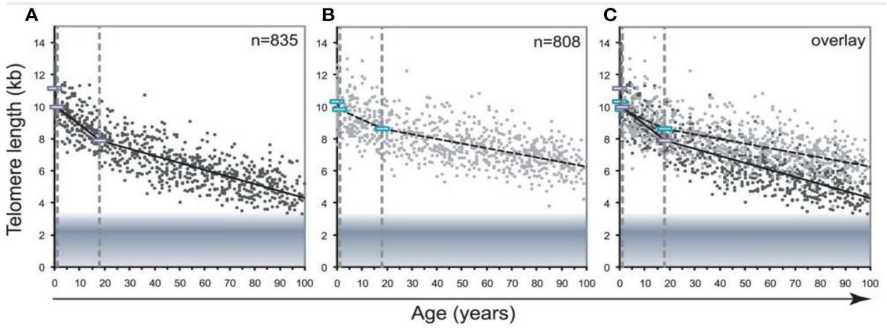
Frequency for Clinical Approved SNPs Associated with Age-Related Diseases



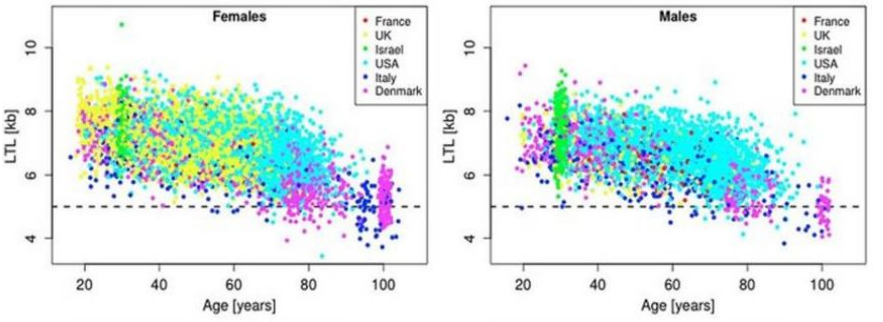
The **single gene mutation** are used for diagnostic the risk of age-related disease such as **Diabetes, Glaucoma, Stroke** etc. Most of disease associated genes are rare with **GMAF** (Global Minor Alele Frequency) less than 0.001. Another polymorphisms are more popular and make **significant impact** in disease development in elder patients (>60 years). Analysis of **ClinVar Database** and literature lets us select more **important genes** which can **implicate health in young people** and **accelerate their aging**: **GCK** (glucokinase), **HNF1A** (hepatocyte nuclear factor-1 alpha; HNF-1α), **PMM3** (phosphohexomutase), **PTH** (parathyroid hormone), **ABCA4** (ATP-binding cassette), **FNDC3B** (fibronectin type III domain containing 3B), **MYOC** (myocilin), **REST-NOA1** (nitric oxide-associated protein 1), and **NOTCH3** (notch receptor 3). This is only a sample of genes selected for the most frequent disorder in old people.

Telomere Length as a Marker of Biological Age: Issues and Limitations

Decline in TL with Age Differs Between Lymphocytes and Granulocytes



Decline in TL with Age Differs Between Countries



Telomere Length can only provide a rough estimate of aging rate, according to studies, and is scarcely a clinically meaningful marker for aging and longevity.

Several unresolved issues are currently impeding the adoption of telomeres as a routine marker in clinical practice. The significant **inter-individual variability of telomeres** is a critical issue. Also, telomeres might **differ between various tissue types**. Moreover, depending on the sampling site, telomeres can **vary even within the same organ**.

It's also unclear whether results from circulating leukocytes can be extrapolated to other tissues. In addition, the rate of age-related telomere attrition **differs significantly between different types of leukocytes**.

However, **telomeres could be a very informative biomarker when used along with other markers**. For example, in a combined cohort study, telomeres and DNAm clock explained 2.8 and 28.5% of the variance in age, respectively, and 29.5% when they were combined.

Source: Telomere Length as a Marker of Biological Age: State-of-the-Art, Open Issues, and Future Perspectives

Clinical Trials And R&D Notable Cases

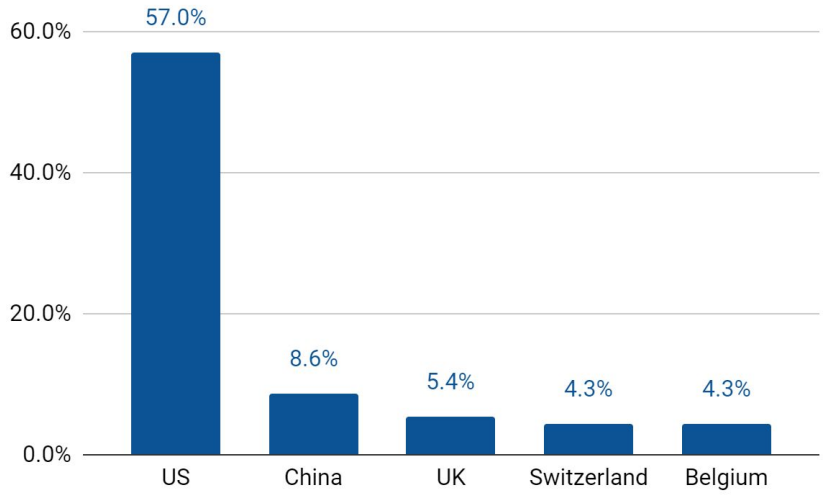
XVIVOS is focused on developing novel algorithms and user-friendly interfaces for analyzing in vitro (or ex vivo) Big Data from high-throughput assays which are applicable to personalized medicine. In the process of achieving this, XVIVOS works with researchers and pharmaceutical companies to improve the analysis platform. The goal of XVIVOS is to integrate these data with pharmacogenomics, in order to discover the best drug for each patient. Further, XVIVOS also facilitates relationships between patients and researchers to assist with novel drug discovery when no current therapies exist.

Salimetrics' assay kits and CLIA-certified testing services are used to measure salivary analytes related to stress, behavior and development, inflammation, sleep, reproduction, health and immune function. Salimetrics continues to be a key partner in bringing best-in-class solutions to salivary bioscience research. By using Salimetrics, researchers can find and implement solutions where the full potential of salivary measures have yet to be realized.

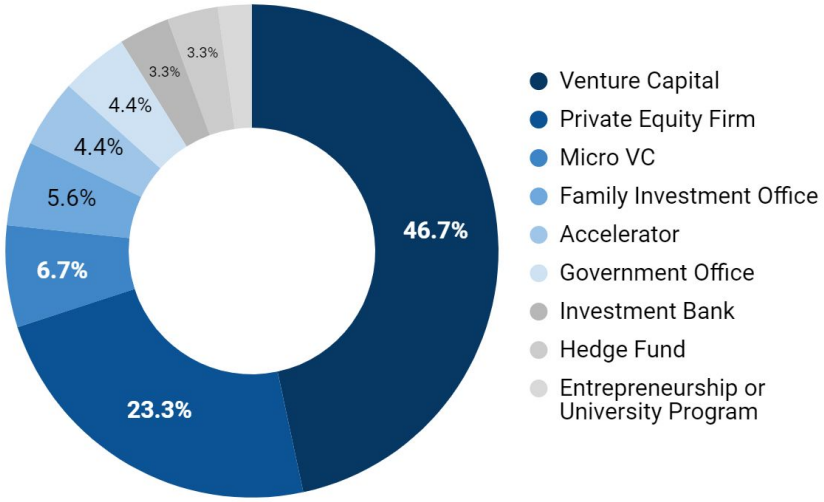
Swiss DNAlysis offers genetic tests developed by our experts in various fields. Laboratory analysis and storage exclusively performed in Switzerland accredited by Swiss Federal Office of Public Health following Swiss patient data protection rules, eligible for coverage by health insurance. Next-generation sequencing technology, confirmation of positive tests with Sanger sequencing, double-checking of negative results with MLPA, evaluation of mutation significance with several databases.

Market Overview: Global Market and Investors

Countries with the Largest Number of Investors, %



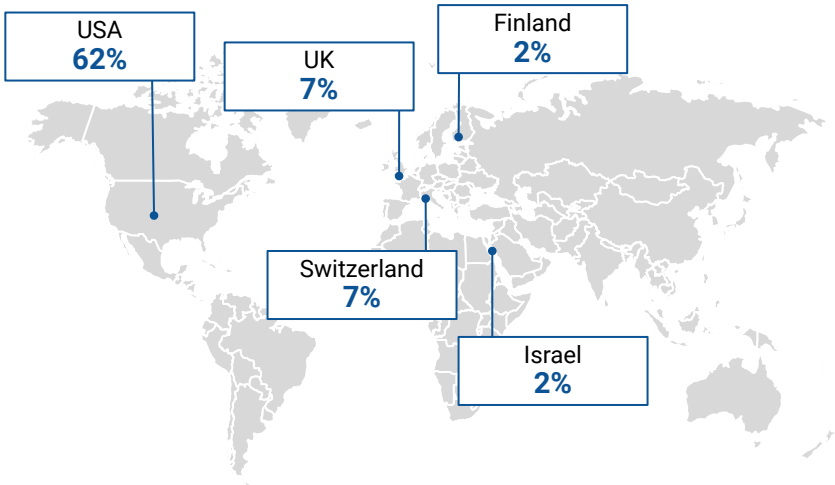
Main Type of the Investors, %



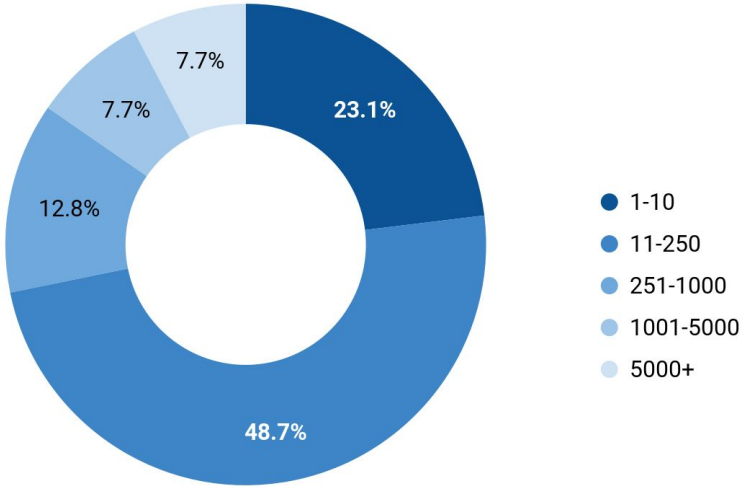
The main part of the investors in Molecular Biomarkers are from the **United States** and accounts for **57%** of the total investors. Investors from **China constitute close to 9% o**f total number of investors. The rest of countries from top 5 by number of investors are European countries: **the UK (5.4%), Switzerland, and Belgium (by 4.3% each)**.
Venture Capital and Micro VC constitute more than a half of all investors **(53.4%)**. **Private Equity Firms** are around **23.3%** of all.

Market Overview: Geography of Companies

Distribution of Companies by Country, %



Distribution of Companies by Number of Employees, %



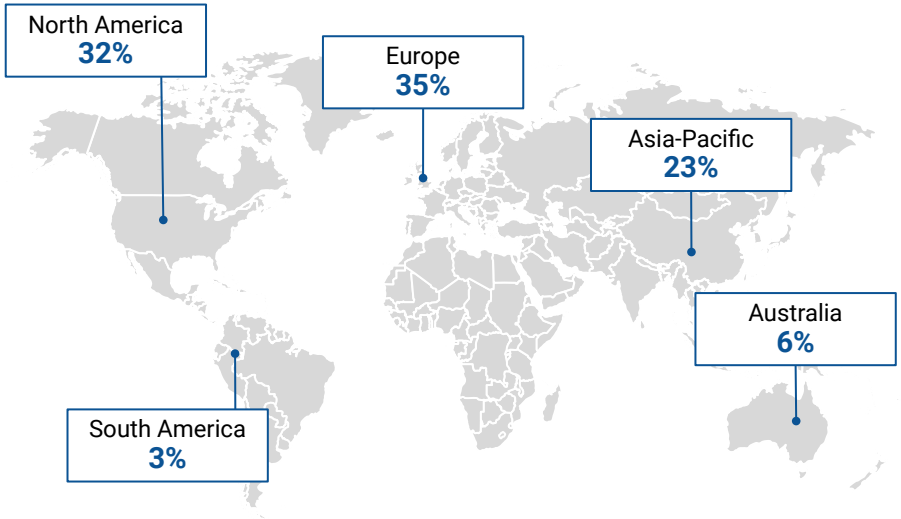
There is thigh geographic concentration of companies involved in the Molecular Biomarkers area - **90% of companies are allocated in the top 5 countries. Close to 62% of all companies** that conduct activities are **from the USA**. **Other 26%** are from **Europe**: in particular by 7% is in the UK and Switzerland each and 2% is in Finland.

Around a quarter of all firms (23%) are **micro-sized** with 1-10 employees, the other **49%** of companies have **no more than 250 employees**. However, there is **close to 8%** of large companies with **more than 5000 employees.**

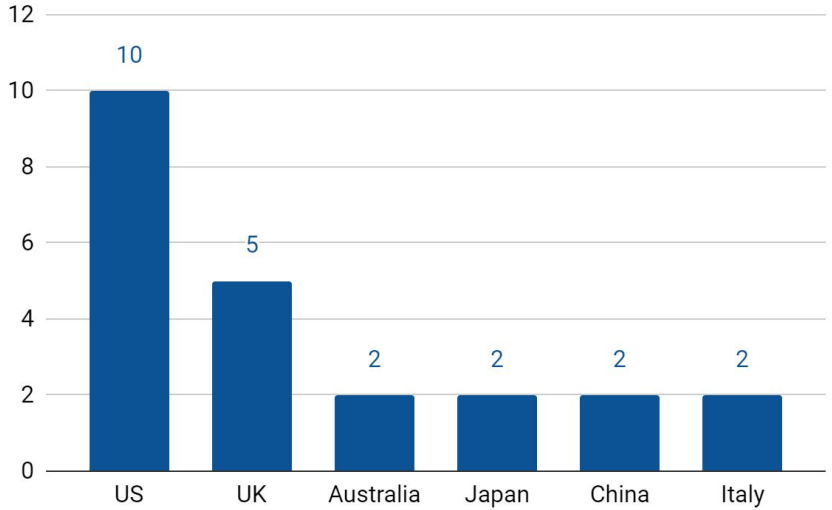
Source: Aging Analytics Agency analysis

Market Overview: R&D Centres

Distribution of R&D Centres by Region, %



Top Countries by Number of R&D Centres

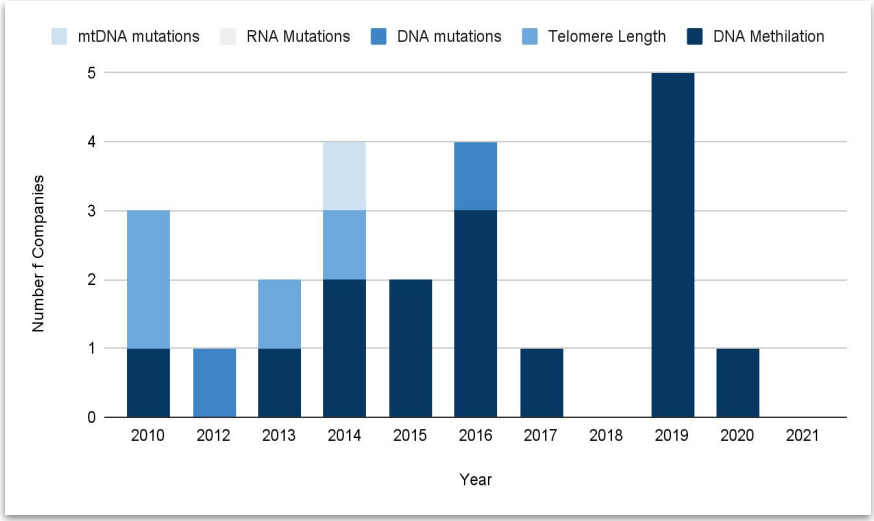


R&D Centres that conduct research on Molecular Biomarkers are distributed all over the world. However, two-thirds are concentrated in North America and Europe, with the other **23% in Asia-Pacific**. **Around 6%** of R&D Centres are **in Australia**, **while 3% (2)** are in **South America.** There are 10 R&D centres in the US and half as much in the UK, which makes these countries centres of R&D activities in the Molecular Biomarkers area.

Source: Aging Analytics Agency analysis

Market Trends of Molecular Biomarker for Aging Diagnostics

New Companies: Molecular Biomarkers



Key Market Trends

- Development new biomarkers
- Growth the number Epigenetic testing
- Early diagnostics of age-related disorders
- Growth of direct-to-customer market
- Digitalization

How it is shown on graph for the last decade all new companies produce **Epigenetic tests**. This type of tests replaced other genetic tests even at-home-tests of Telomere Length which are saled directly to the customers. More than **50%** analyzed companies don't present detailed information about their founds, localization of head quarter and year of foundation. These companies often **don't have own product/test kit** and **do analysis in outsourcing laboratories**. High cost on genomic research equipment and complexity in predictive genetic testing are major factors that may restrain the market to a certain extent going ahead. Moreover, lack of trained professionals and inadequate funding are expected to create further challenges for market growth.

Key Takeaways: Molecular Biomarkers

Genetic testing helps to **predict future risk of disease** and offers information and data about the genetic makeup of a child. In the market more than **50% share Epigenetic tests** for prediction biological age via measuring level of **Methylated DNA** and **Telomere Length**.

The **Direct To Consumer segment** is expected to hold largest market share over the forecast period due to growing awareness related to at-home genetic tests. The most companies are located in **USA (>65%)** , **Europe (17%)** and **Switzerland (7%)**.

This **market develops slower** in comparison with other biomarker markets. The **increasing focus by governments** of various countries, to regulate and create awareness regarding genetic tests, has successfully resulted in the **faster adoption of these tests** across the world but presence major players in the market has created a **strong entry barrier for new entrants**.

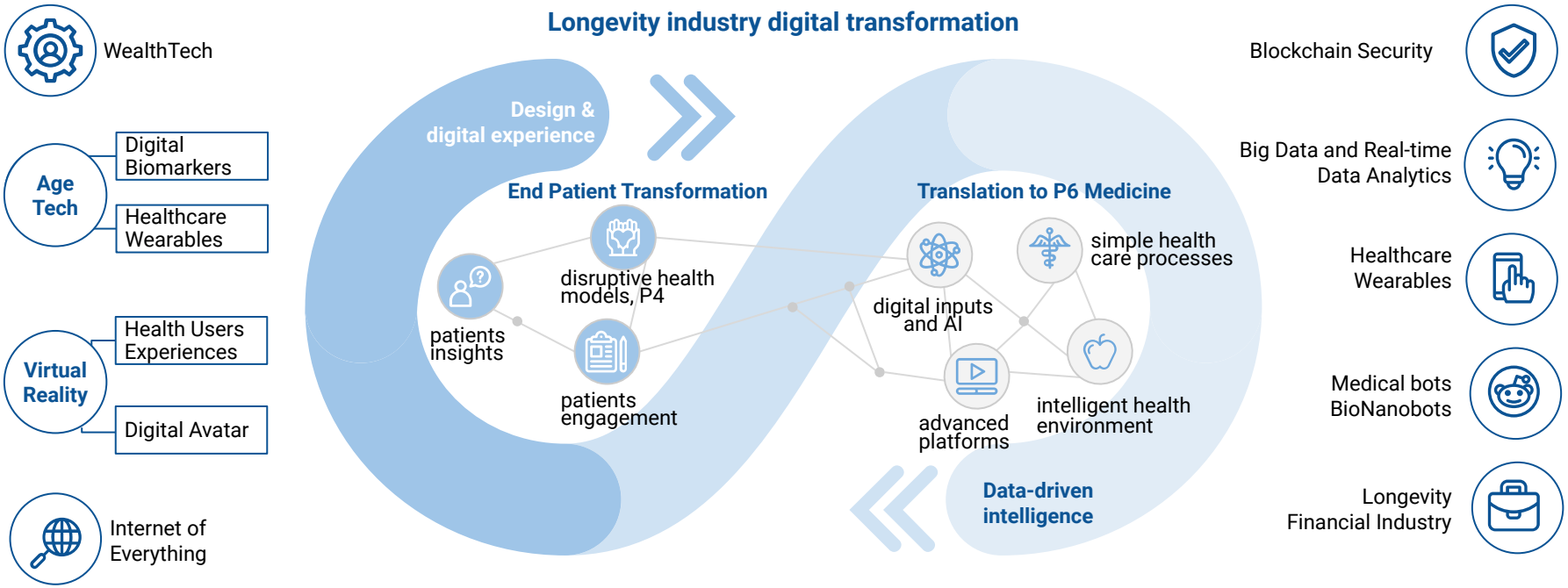
Genetic and Epigenetic testing are in priority and many companies **offer at-home test** for **healthy living** and **wellness diagnostics**. Customer directed companies often **don't have own product/test kit** and do analysis in **outsourcing laboratories**.

High cost on genomic research equipment and **complexity** in predictive genetic testing are major factors that may **restrain the market** to a certain extent going ahead. Moreover, **lack of trained professionals** and **inadequate funding** are expected to create further **challenges for market growth**.

Many **diagnostic panels** include **clinically approved polymorphisms** as well as **investigational molecular biomarkers** without appropriate study on clinical populations. It makes a risk for customers to get **non-reliable information** with **incorrect interpretation** of diagnostic results.

The Next Frontier: Towards a “Digital Avatar”

Digital Transformation of the Health and Longevity Industry



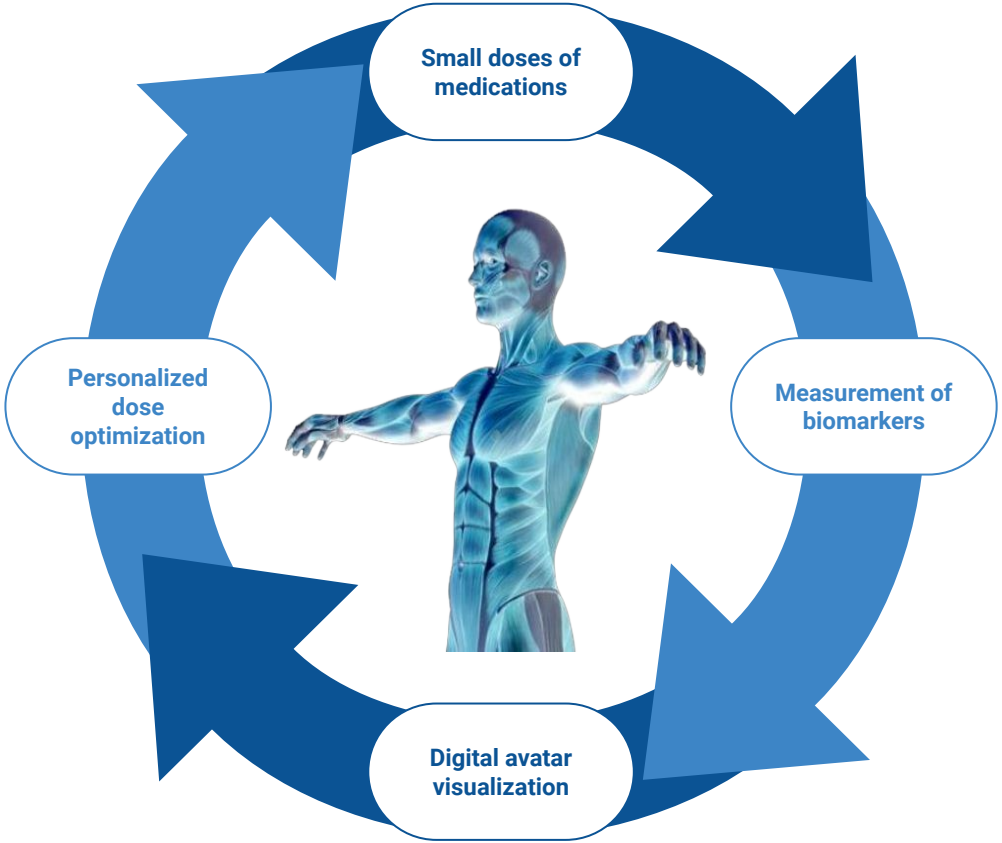
The future of health will be driven by digital transformation enabled by radically interoperable data and open, secure platforms. Radically interoperable data and AI can empower consumers in ways that are difficult to visualize today. Data about individuals, populations, institutions, and the environment will be at the heart of the future of health.

Source: Image: Modified from Everis

Biomarkers and Data Science in the Core of P4 Medicine

Not only new methods of standard industry benchmarking and forecasting need to be developed to **combat the issues of overcomplexity and multidimensionality in the Longevity Industry,** but new methods of testing the basic safety and efficacy of Longevity and Precision Health prevention, diagnostics, prognostics and therapeutics need to be adapted as well, **moving away from the use of model organisms,** towards a more human-centric approach.

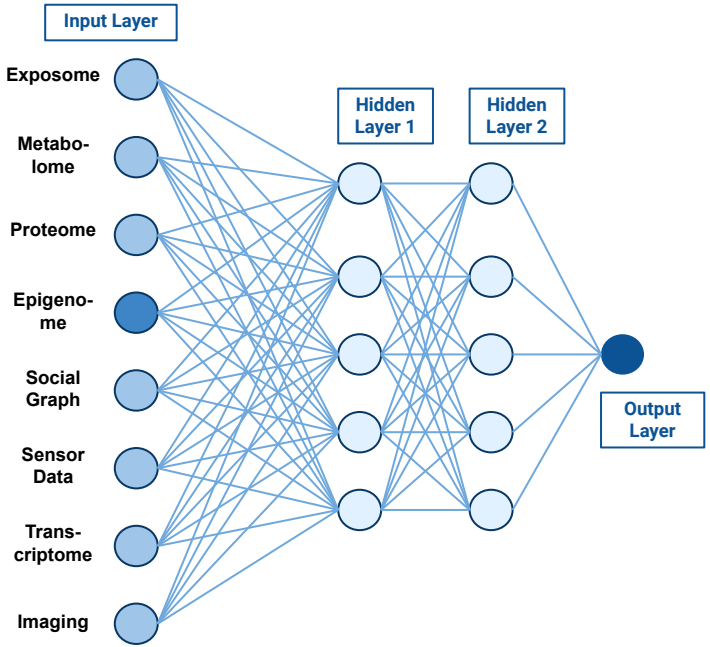
Digital biomarkers satisfy all these new industry requirements: they can be continuously tested on all users, notifying adverse micro-effects and ultra-stratifying patients. Total precision of complex tests is granted by magnifying the number of possible measures, the only possible actionable way of creating big enough dataset is development of **digital avatar**.



Data Science and AI Making Complex Biomarkers Available

Unlocking the value of **epigenetic data** for actionable insights will drive aging research, precision medicine, and ultimately population health. Fundamental questions should be addressed by integrative personal **omics** profiling with epigenomics at its center, combining genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from an individual to reveal dynamic molecular changes in health and disease. With the evolution of better technologies and digital capacity, enormous amounts of *omics* data will be produced and stored in the digital space and researchers will need AI to be able to keep track of it. AI is already transforming **the world of medicine** and will help healthcare providers make faster and more accurate diagnoses. Based on epigenetic data, deep learning algorithms will predict the **risk of a disease** in time to prevent it and will help scientists understand how interindividual epigenetic variability leads to disease. However, ensuring security and privacy in transmitting and storing personal epigenetic profiles will require building a new and open multi-omics data ecosystem. **Blockchain, an open-source technology** that uses a distributed database for secure transactions, has the potential to address many of the challenges related to security and privacy with personal health information. Blockchain technology enables integrating data from a distributed network of participants in the healthcare value chain on a global scale.

Multilevel artificial neural network to support epigenetics research.



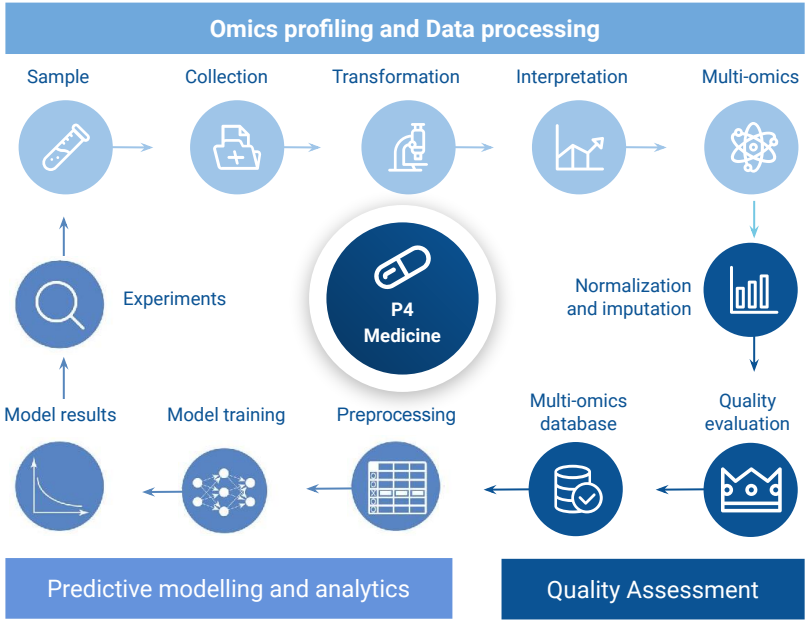
Note: At the input layer, multi-omics and demographic data are fed into the network. Each circular node represents an artificial neuron and each line represents a connection from the output of one neuron to the input of another. Machine learning enables data-driven decision systems to continuously learn from new epigenetic data and adapt itself to deliver "reliable and repeatable" results.

Source: Schumacher. Epigenetics of Aging and Longevity. 2018.

Data Science and AI Making Complex Biomarkers Available

Machine and Deep Learning, systems health and multi-omics technologies revolutionize the way we acquire and process data. At their core, **AI algorithms** dissect the data to learn their structure and associations within, often without the need of specific knowledge on processes and models that generated them. The strength of AI techniques is proportional to the size and quality of the data amassed. At the same time, sequencing and molecular technologies can generate a vast amount of **high-quality data** in an inexpensive, reproducible way and hence they allow an unprecedented system-level view of any organism. These datasets, which can come from a variety of sources, equipment and experimental settings, are in their majority not ready to serve as training sets to computational models, Machine and Deep Learning methods, as they have not been created with that function in mind. As such, there is a clear need for methods that process, normalize, integrate and transform the plethora of heterogeneous multi-omics data to cohesive compendium that can be used as a training grounds for further analysis and learning.

Machine and Deep Learning analytics has been applied in biology to deal with the intrinsic complexity in omics data with a long history and its integration in recent years. The high-level overview of the machine- learning analytic pipeline for integrated multiomics data consists of data preprocessing, modeling, and active learning. Once a model is constructed and evaluated, active learning guides what experiments to perform next to minimize uncertainty in the model.



Three major steps involved in AI-driven multi-omics: Data acquisition, multi-omics integration and predictive modeling. An end-to-end pipeline for *multi-omics* data as a source of biomarkers for health care, biological age precise calculation and extension of lifespan.

Source: Kim et al. Data integration and predictive modeling methods for multi-omics datasets. 2017

AI and Digital Platforms: Towards a “Digital Avatar”

Mobile Devices

AliveCor

Cardiogram

Apple

Fitbit

Xiaomi

Data from device

Machine learning

Mobile apps and platforms

Insilico Medicine
Aging.AI

Facelytics

122 LABS

ALTIS LABS

Haut.AI
PhotoAgeClock

Haut.AI
Haut.AI Skin Health

INSILICO MEDICINE

PROSCIA
Proscia Platform

iCarbonX
ICabonX Platform

PathAI
PathAI Platform

CarePredict
CarePredict Platform

zipongo
Digital Nutrition Platform

Tempus Platform

Designed for health

freenome
Freenome Platform

Floro'clock

nourish balance thrive
Blood Chemistry Calculator

YOUNG.AI

Eterly

zebra
AI-Powered Radiology Assistant

enlitic
Enlitic Platform

Better
THERAPEUTICS
Better Therapeutics Platform

ada
Ada
Symptom Checker app

Onegevity Health

DeepMind Health
Google`s DeepMind Health AI Platform

MeBio App

BenevolentAI
BenevolentAI Platform

KenSci

xsensio

Haut.AI

babylon
Babylon Health Platform

InsideTracker

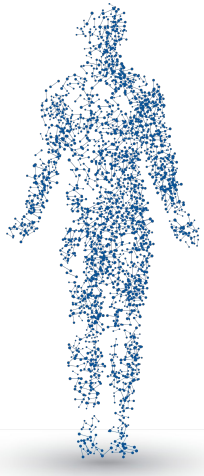
biocanic

SEQSTER

RYNKL

LIFE Extend

LifeOmic



Digital Avatar

Longevity Biomarkers and Financial Industry

Biomarkers for Financial Market

The value of the information derived from the biomarkers cannot be reduced to the scientific only. Many **financial instruments can be optimized using biomarkers-based longevity and/or mortality indices.** Such instruments show great value for a whole variety of entities, both governmental and privately held, providing optimized hedging solutions.

Besides different types of financial instruments, biomarkers assessment can become a **crucial part of the valuation and due diligence processes for Longevity- and Pharma-related companies.** It is well known that companies participating in drug development are highly exposed to the risks related to the human validation (i.e. clinical trials). It is often hard to predict and assess whether a solution provided by a given company is relevant to the market. In this case, biomarkers-derived information might play a crucial role in the assessment of the company's performance, allowing to evaluate how its services affecting human Longevity.

These two different approaches suggest great improvements in the financial market enabling **optimized risk management** both in terms of Longevity risks hedging, and investment risks reduction.

Who can benefit?


Independent Financial Advisors


Private Equity Funds

Private Banks & Wealth Managers


Corporations


Asset Management Companies


Venture Capital Funds


Challenger Banks


Retail Banks


Pension Funds


Insurance Companies

Longevity Risk / Longevity-derived Financial Instruments

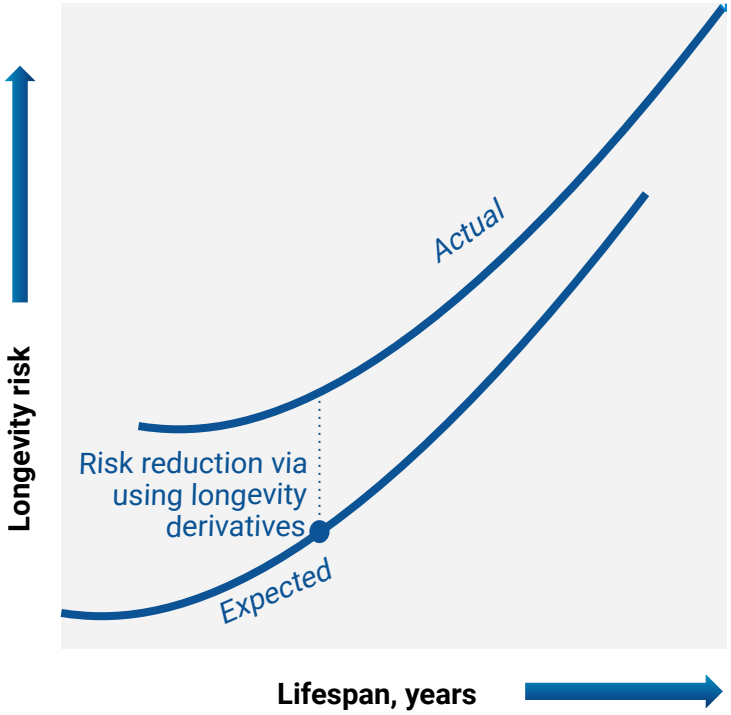
A new global capital market, **the Life Market,** is developing and "longevity pools" are on their way to becoming the first major asset class of the twenty-first century. **Longevity risks arrive due to inaccurate predictions of the level of mortality rate and numbers of retirees.**

Thus, **Longevity-derived financial** instruments are used in order to hedge such risks. In general, these derivatives are designed to **generate income for investors due to increased Longevity,** as well as reduce the negative impact for companies suffering from Longevity risks. Longevity risks have a weak correlation with other financial risks.

Although the **Longevity Derivatives Market has many economic agents,** the main ones are **hedgers** (pension funds and insurance companies, have an incentive to transfer Longevity risk off their books), **speculators,** and **arbitrageurs** (investment banks and hedge funds are interested in acquiring exposure to longevity risk since it has a **low correlation with classic market risk factors,** therefore small beta coefficient attracts investors a lot).

New opportunities are opening up for all these agents because of the increased accuracy of risk assessment and forecasting and selection of the correct risk management tool.

Hedging with Longevity Derivatives

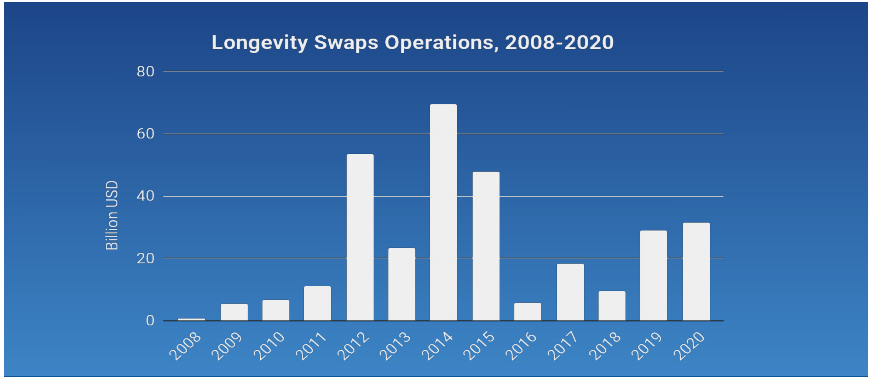


Source: Longevity Derivatives and Financial Instruments

Longevity Risks for Companies and Governments

Longevity risks are of great interest for both governmental and private institutions

The graph below depicts the dynamics of **longevity swaps' operations** in the period of 2008-2020 years. During this period, deals for the amount of $313 billion had been struck. The amount of new operations correlates with life insurance market size. For example, the insurance market size in the US also significantly dropped after the 2015 year and slightly recovers during the 2016-2020 years (IBISWorld, 2020).



Governments tend to have **a two-dimensional interest in Longevity securities.** First, **for hedging** financial institutions sensitive to such risks, second, **for securing** its own exposure, as it is a significant holder of the Longevity risks: via the pay-as-you-go state pension system; via its obligations to provide health care for the elderly and for other similar reasons.

Ensuring an efficient annuity market and efficient capital market for Longevity risk transfers means that government can affect and reduce concentration risk and provide construction of national longevity indices.

Government helps **to share Longevity risk fairly** across generations and provides **a fair risk premium.** When issuing longevity derivatives based on biological age, the government could insure age-related diseases and implement more advanced and actionable metrics for pension programs.

Government = Insuring age-related diseases + Minimising of spended resources + Using accurate and realistic health indicators

Sources: Artemis, Longevity Derivatives and Financial Instruments

Longevity Biomarkers Financial Applications

Longevity Biomarkers show a great value for financial market, allowing engineering of optimized financial instruments and implementation of the biomarkers-based due diligence and valuation

As was shown, many financial instruments can be formulated in terms of the Longevity. This implies the importance of the development different quantifiable biomarkers' assessment approaches. As a result, such approaches can be used for:

1. Longevity Risks Hedging
2. Investment Risks Reduction
3. Personal Financial Risks Optimization

It is important, that use of biomarkers in financial areas will positively affect not only institutional or other “big” players. Biomarkers can become a feasible solution for personal risk management too. Additionally, the active implementation of the biomarker-derived data will provide sufficient means for investment risks management, which will optimize the effectiveness of the allocation process. This, in turn, can provide better and more efficient Longevity solutions for the public.

When time is money, biomarkers are the means for wealth management.

Possibilities for Further Improvements

The number of biomarkers of aging and their association with various diseases increases each year, but a critical review of each of them is needed. Understanding that biomarkers of aging Industry development is an ongoing process means that the project needs to be further improved and monitored. For instance, new analytical reports need to be done for creating new accurate and current databases.

The database of firms, investors, and R&D facilities will be enlarged to accommodate new startups and established companies looking to increase their longevity products rollout efforts.

New techs like AI, Omics, and Digital monitoring gadgets assessment in biomarkers of aging Industry will be done to understand their impact on Biomarker Industry advances in general.

An extensive study on products and treatment methods to promote longevity or decrease rates of development of age-related diseases will be undertaken as well.

Multiple forecasts concerning biomarkers of aging Market trends are required to identify all aspects and further development of companies in longevity field. They are also needed to understand which forecasts were proven to be true in order to optimize our analyzing strategy.

Avenues for Further Improvement in the Second Iteration of the Project

- Database Expansion
- TRL analysis of each documented test or platform
- Updates on the Most Notable Longevity Companies
- Follow-up on Predictions Made in the Previous Iteration
- Increase Number of Deeply Studied Cases
- Separate Research on Longevity Biomarkers Development
- Deep Analysis of AI and Omics-tech Implementation
- Broad Assessment of New Longevity Startups
- Current Monitoring of Longevity Biomarkers Trends

Conclusions

Conclusions

High demand for personalized medicine leads to rise in commercial interest and government support for Age-related Biomarkers and AI-technologies for Longevity. That trend accelerates strong funding of Longevity sector thus promoting faster innovation.

The amount of **clinical and biological data** in the world is steadily rising, with a projected **CAGR** of more than **30%.** The n**umber of datapoints** for clinical usage is **rapidly increasing**, and the only option to optimize their utilization is to create **digital avatars**. A **digital avatar is a forerunner in the field of personalized medicine**, which is still in its early stages. Because of the massive amounts of data, clear **analysis of such avatars is only feasible with the help of AI**.

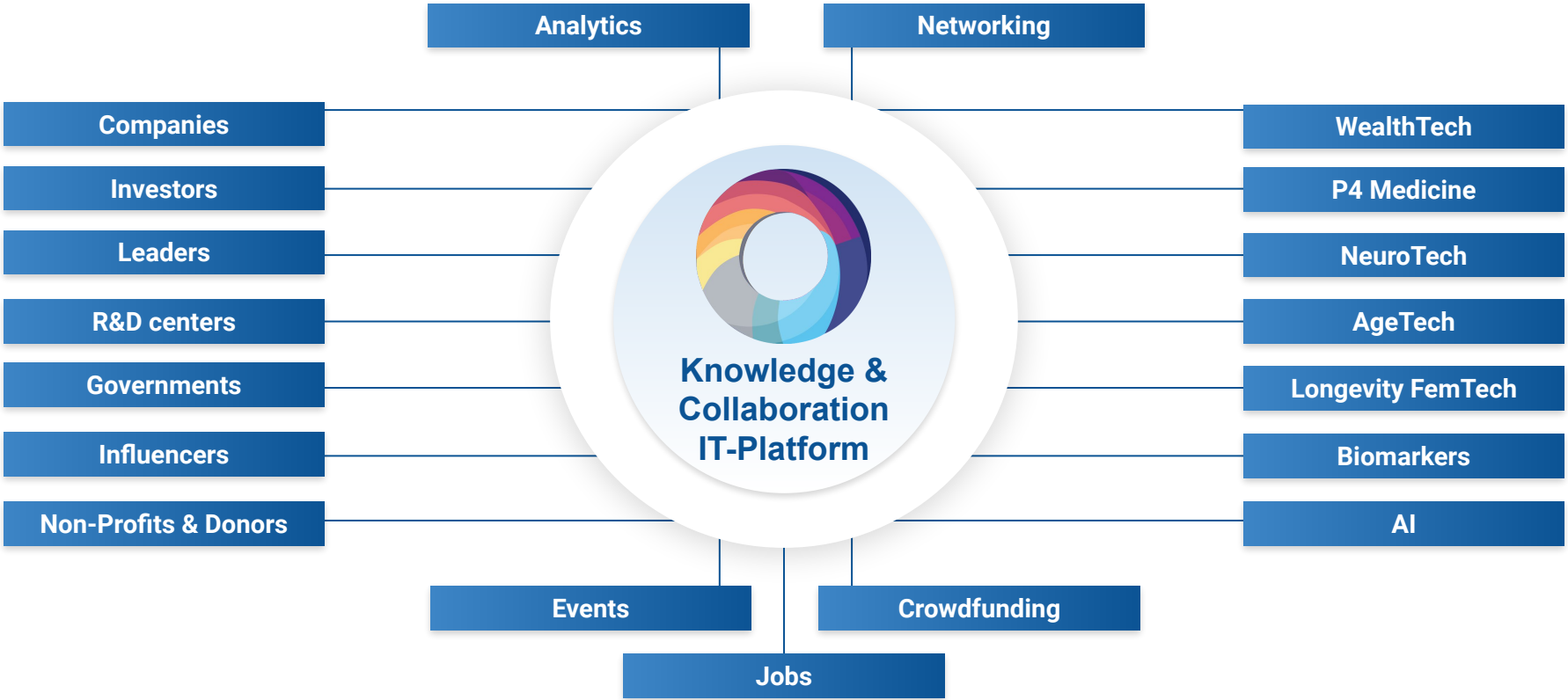
The ability to monitor health status with accurate and trustworthy lab findings explains the market's significant appeal for the **at-home tests**. This **trend emerges** as a result of the **simplified procedure of ordering tests, collecting samples, and obtaining results**. Typically, such solutions arise as a result of the probable **removal of the need for hospital/lab visits,** making such tests an ideal solution for modern people. **This tendency is about to take off on a massive scale, and traces of it can already be observed.**

The **increasing popularity of Artificial Intelligence** leads to the creation of innovative techniques and the digitization of healthcare services. The **use of Artificial Intelligence** possibilities in both **preventative and therapeutic medicine** is a **major trend in the industry**. It is now evident that **AI can be used to augment many operations** in order to **save costs and enhance overall results**.

AI for Longevity will become one of the most impactful sectors within the industry in the next several years, and make its potential to accelerate the continued development of the industry in almost every sector, such as **Longevity R&D, therapeutic development, P4 Medicine, biomarker discovery**, and even non-biomedical sectors such as the **Longevity Financial Industry**.

Longevity risks are an important component of the **financial sector**, and as the **population ages**, their prevalence grows larger and more impactful. Because of the progression of the longevity industry, a lot of **innovation is altering the paradigm of longevity risk assessment**, which might possibly **lead to significant changes in the longevity financial sector**. As a first sign of such transformation, new derivatives and risk assessment approaches are developing.

Longevity.International: One-Stop Platform for Longevity Industry Knowledge



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