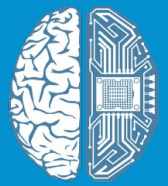
Biomarkers of Longevity

Analytical Report

Current State, Challenges and Opportunities
Landscape Overview 2019

Increasing Role of Data Science and Artificial Intelligence in Biomarker Discovery and Monitoring

AGING ANALYTICS AGENCY



DEEP KNOWLEDGE GROUP

www.aginganalytics.com

Table of Contents

Executive Summary

Executive Summary

"Biomarkers of Longevity: Current state, Challenges and Opportunities Landscape Overview 2019" **is an open-access special analytical case study by Aging Analytics Agency that uses comprehensive analytical frameworks to rank and benchmark existing panels of biomarkers of aging, health 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; providing advice to the industry for the conception, development and maturation of their action plans, and to policy makers in order to combat the problem of Ageing Population and realize that opportunity of National Healthy Longevity.**

The use of biomarkers is an indispensable component of industry analytics and assessment. It is the foundation upon which measurement of Healthy Longevity and the effectiveness of P4 Medicine, Regenerative Medicine and Longevity therapeutics are built. In this sense, the present report is designed as an in-depth review of the state of the art in biomarkers of biological age R&D to advise accurately the market, industry and public sectors. It was produced to offer a panoramic review of the global landscape of aging and Longevity biomarkers, containing selected lists, rankings and enhanced profiles with more than 70 Single Biomarkers directly correlated with the trajectories of age-related diseases and geriatric syndromes and exceeding 100 diverse Biomarker Panels for analytical science-driven comparisons that allow an optimal integration of multiple biomarkers for practical uses, such as drugs discovery and development for Longevity, Longevity therapies development, enhanced and sophisticated aging health monitoring in precision clinics, or development of digital environments aimed at assessing the aging trajectory to mention some particular utilities.

The purpose of the approach offered here is to facilitate the achievement of highly actionable monitoring systems for healthcare in general, and for healthcare during aging in particular; the beneficiary sectors are multiple, including clinical practice itself, but also translational research initiatives, frontier development frames that exploit the current conditioning of the mature field of Longevity, investment intentions in a market with the highest complexification rate in human history, and administrative initiatives for policy programs pointed to health promotion and precise prevention of age-related diseases, whose design and consolidation according to the subsequent criteria will guarantee a renaissance never seen before in economic and social dynamics.

In addition to their purely descriptive and analytical approaches, the report is designed to make key strategic recommendations, advice and guidance regarding biomarker implementations, technologies and techniques, within the reach of companies, other entities, and nations, in order to assist them in optimizing their action plans and strategies, providing specialized guidelines for business and investment core decisions.

Executive Summary

Based on the results of this analysis, the special case study presents its formulation of an ideal Minimum Viable Panel (MVP) of Longevity biomarkers: a panel of biomarkers which though not as precise as possible are precise enough and easily implementable. The report also presents a “most comprehensive” list of biomarkers of aging, devotes analysis to recent novel biomarkers of aging just entering R&D processes today, and highlights the core conclusion that uses of Digital Biomarkers and AI in biomarker discovery, development and assessments will come to be a necessary and indispensable component of Longevity Industry as the volume of data on both biomarkers and the complex networks of how they interact together continues to grow.

The report also delivers extensive profiles of single biomarkers and whole panels: their advantages and strengths, disadvantages and weaknesses, and future perspectives, challenges and opportunities with a focus on technologies currently used for assessment; concrete analysis of routine, advanced and novel biomarkers of aging, emerging tools and platforms, and insights about the impact of these biomarkers on health systems and clinical practice. The central purpose of those characterizations is to submit practical conclusions and recommendations regarding the Most Comprehensive and Most Viable (or Minimum Required) single biomarkers and panels of aging for their immediate implementation, either in biomedical research, therapeutic development and clinical trials, P4 Medicine and overall clinical practice, emphasizing the intersection between this wide new market, digital environments designed for real-time integration of aging and Longevity health metrics, and the new possibilities offered by AI platforms. The ultimate intention of Aging Analytics Agency is to solidly establish the relative and absolute usefulness of these presentations for precise and actionable measurement of biological age and enhanced assessments of health status, age-related diseases, geriatric syndromes, and Longevity.

As the scope of P4 Medicine broadens actively and healthily, the number of biomarkers, measurement technologies and platforms will increase rapidly to the thousands in the coming years; this will provide the opportunity to improve medical stratification to its maximum degree reaching Personalized, Participatory, Precision and Preventive Medicine for both, non-healthy populations and the healthy and young; also, to achieve the conditions for exhaustive and precise studies with samples of only one individual and allowing to prescind from conventional model organisms for biomedical research, due to the enormous flow of biological digital data that will be extracted continuously, individual to individual. These vast amounts of biomarkers data in the form of zeros and ones will make impractical the implementation of P4 Medicine by current, manual means; the construction and evaluation of massive networks of interconnected biomarkers will be carried out by highly specialized digital systems in pattern recognition, trained with aggregate information from hundreds of thousands of individuals minute by minute. Prototypes of these systems already exist, and are beginning to be implemented today.

Executive Summary

Aggregation of biomarkers of Longevity, rather than biomarkers of disease only, and from healthy populations - among the young and the even younger, rather than bedside data from the hospital populations, will be part of everyday life due to the novel Digital Health platforms capable of extracting truly massive amounts of clinical relevance data from a single patient through electronic layers.

These transformations already underway in biomarkers assessment modality will allow to move from the conventional therapeutic approach toward large-scale precision preventive medicine, the necessary vehicle to build both individual and national Healthy Longevity; and this will also be the foundation for the achievement of a unified theory of the root causes of aging and Longevity. The one plus the other, these two emerging together, will provide -are providing- a framework to intervene the process of aging, in a rather accelerated way than gradual. Tech companies rather than healthcare companies will play the leading role in this process; the threshold is already blurring. The use of AI will give sense to the thumping amount of digital biomarkers data, and it will allow the development of undoubtedly multiple optimal biomarker panels for the monitoring of aging and its correction, as well as countless other health biomarkers (digital and non-digital) for AI-driven analysis of each person's deep health status, allowing to orchestrate extremely personalized therapeutic interventions in response to minimal and currently imperceptible fluctuations in all those biomarkers. As the number of data points increases, AI-driven analysis will be strictly necessary in the Longevity industry and the health industry as a whole.

At this point, it is impossible to determine whether biotechnologies for Longevity have been successful if we cannot tell how advanced the aging process is in any given individual; but at the same time the latter will not be feasible until successfully achieving highly actionable Panels that allow to evaluate the aging process in broad healthy and less healthy differentiated ranges of the population spectrum. Is in this sense that Biomarkers are an essential factor in Aging Analytics Agency's strategic agenda, which includes recommendations for the establishment of AI centres in the United Kingdom, the indispensable medium to nail down the implementation of P4 Medicine and also to guarantee competitiveness in this new global health market, in the same way that highly specialized advice for the success of longevity-related government initiatives worldwide. It is important to develop and promote the widespread use of a comprehensive enough Panel of Biomarkers but, primarily, immediately actionable. We have documented many of the aging Biomarkers here and identified from among them those which, by the metrics described - and never reported in pre existing literature-, belong to this category we have named Minimum Required: the Most Viable Products for immediate implementation.

It is our hope that regardless of whether it is adopted wholesale, this entire work may serve as a starting point for discussion on how best to utilize the deep knowledge we already have to maximum effect on health of aging populations and aging economies, as soon as possible.

Methodology

The significance of biomarkers in the Longevity Industry is central since they are the primary metric in Geroscience, Regenerative Medicine, multiple AgeTech implementations and especially in P4 Medicine. Biomarkers also provide the prime source of data for the AI for Longevity industry, Drug Discovery and Development, Clinical Trials and for Translational Research. For these reasons, standardized metrics are needed to evaluate the biomarkers and the Panels that occupy us.

Within the scope of the report, the following methodology will be implemented, outlining the quantitative evaluation approach:

Accuracy Assessment

- It is a measure of the precision of the Single Biomarker or the Panel to predict overall biological age
- Its magnitude depends on the *number* of biomarkers evaluated by the Panel, the *nature* of those biomarkers, the *scientific background* of its direct association with age-related conditions and processes, and *qualitative characterizations* that assigns or removes scores

Availability Assessment

- It measures only the material capacity of extensive implementation for the reference character; i.e., for the single Biomarker or the Panel
- That material implementation capacity is understood as an expression of *market availability* of assays, tests, technologies or platforms, its *invasiveness*, *monetary value*, and the proposed classification framework for *qualitative characterizations* used also in Accuracy Assessments

Actionability Assessment

- Actionability is an expression or combination of both the accuracy and availability of a Biomarker or a Panel
- Actionability Assessment allows to evaluate not only the current material capacity of implementation of a biomarker or a Panel but also its viability for biological age prediction in such an immediate and effective frame of implementation, thus empowering Single Biomarker and Panel comparisons with a purely pragmatic sense

Such precision assessment will maximize the capacities of decision-makers to increase the efficiency of public health programs and policies, as well as decision-making processes in the core of healthcare industries.

Report Value Proposition

1. **What are the current most comprehensive biomarkers and panels to follow the aging trajectory and its related conditions and the most viable or minimum required ones, and how they can be implemented in the most ideal and useful manner?**
2. **What leading personalised and preventive market-ready health assessments can aging biomarkers and panels dispense to the existing pipeline of healthcare entities to maximize their competitive advantage?**
3. **What novel updates and advances in biomarker-related research and development will impact the health industry in the next years? Which of those should be watched closely for integration into clinics and biomedical or healthcare companies' existing pipelines as soon as their conditioning is achieved?**

We feel that our efforts over the course of the past five years have established a solid foundation of knowledge and expertise upon which we intend to summarize the entire landscape of aging and Longevity biomarker utilities in the health industry: the production of this new report entitled ***Biomarkers of Longevity Landscape Overview 2019: Current State, Challenges and Opportunities.***

This report seeks to answer these three specific questions, with an upcoming +300 pages version that will be produced over the next 3-6 months, and a new edition of its content during each financial quarter, incrementally increasing its breadth and depth as we go along, and with each edition providing a deeper, more comprehensive and more precise understanding of the landscape. It will deliver:

- Concrete deep analysis of which biomarkers and biomarker panels are available today; its strengths and weaknesses, their accuracy, availability and current actionability, and the opportunities and challenges related to its uses for real-time and precision monitoring of health status, and ultimately the reversal of 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;
- Highlights regarding the role of digital biomarkers and AI platforms and how they will become necessary and indispensable components of ageing and Longevity biomarker discovery, research, development and users daily use;

The parties who will have early access to this report will gain deep expertise on how they can optimize their clinics' strategic, technological and scientific prospects in order to deliver the most sophisticated and comprehensive precision health products and services for their clients.

Biomarkers of Longevity

1st edition. Selection and Current Status, 2019

Approved for Clinical Use - 41
Research Use Only - 45
Healthcare-Ready - 33

Approved for Clinical Use

Healthcare-Ready
(waiting for clinical approval)

Research Use Only

Biomarker Panels

- InsideTracker Inner Age
- InsideTracker Ultimate Plan
- aCGH RGCC
- Immune-Frame
- Comprehensive Adrenal Stress Profile
- B-Cell Memory and Naive Panel
- Natural Killer Cell and Natural Killer T-Cell Panel
- Health + Ancestry Service
- Carnitine Panel
- Cytokine Panel, TH1
- Hepatic Function Panel
- Regulatory T-Cell Panel
- Cytokine Panel
- Oxidative Stress Analysis 2.0
- Adrenal Check
- Adrenal Stress Profile
- Advanced MethylDetox Profile
- Advanced MethylDetox Profile + Thelomere Length
- AGE-Reader mu Test
- Cytokine Panel
- biobank Biomarker Panel
- Aging Theranostic 1.0
- 10 Hormone Saliva Test Kit
- Anti-Aging #4 Comprehensive Blood and Urine Test Panel
- Female/Male Saliva Profile II - Test Kit for 6 Hormone Level Imbalances
- Healthy Aging Panel (Comprehensive)
- CardioGenomic Plus Profile
- ImmunoGenomic Profile
- NeuroGenomic™ Profile
- Metabolic Analysis Profile (Organic Acids)
- PhysioAge Biomarkers of Aging Test

- smartGUT™ Microbiome Test
- Microba Insight™
- GlycanAge Test
- Gut Microbiota Biohacker
- Genetic Age Test
- toxomiRTM biomarkers of toxicity
- osteomiRTM validated bone biomarkers
- thrombomiRTM biomarkers of platelet function
- Viome Gut Intelligence™ Test

- Metabolism Panel
- Immune Response Panel
- Cardiovascular II Panel
- Cell Regulation Panel
- Organ Damage Panel
- Neurology Panel
- Inflammation Panel
- Cardiovascular III Panel
- Neuro Exploratory Panel
- Cardiometabolic Panel
- Oncology III Panel
- Oncology II Panel
- HumanMAP v.2.0
- MetabolicMAP v.1.0
- CardiovascularMAP v.3.0
- DiscoveryMAP v.3.3 Panel
- AngiogenesisMAP v.1.0
- NeuroMAP v.1.0
- ImmunoMAP v.1.0
- Explorer MAP v.1.0
- InflammationMAP v.1.0
- CytokineMAP B
- CytokineMAP A
- LEGENDplex Human CD8/NK Panel
- LEGENDplex Human B Cell Panel
- MiRXES ID3EAL miRNA Assay
- Phospho-H2AX (Ser139) cellular kit
- Senescence Detection Kit
- SPIDER-βGal
- OMIP-004
- OMIP-018
- OMIP-039
- Salivary Cytokine Panel
- LEGENDScreen Human PE Kit
- LEGENDplex Human Th Cytokine Panel
- OMIP-027
- OMIP-007
- OMIP-029
- Human v3 miRNA Assay

Digital Panel Platforms

- Babylon Health Platform
- Ada Symptom Checker app
- CarePredict Platform
- Health Reviser Platform
- Google's DeepMind Health AI Platform
- Centers for Age Control AgeMeter

- Blood Chemistry Calculator
- AI-Powered Radiology Assistant
- MEDIAGE™ Biological Age Measurement System
- KenSci Platform
- Enlitic Platform
- Aging.AI
- Young.AI
- PathAI Platform
- Buoy Health Platform
- PhotoAgeClock
- Haut.AI Skin Health
- Digital Nutrition Platform

- Proscia Platform
- Freenome Platform
- BenevolentAI Platform
- Better Therapeutics Platform
- Tempus Platform
- ICabonX Platform

Single Biomarkers

- CD4+ T-Cell Recent Thymic Emigrants
- CD57+ NK Cells, Peripheral Blood by Flow Cytometry
- CD21 (Dendritic Cell) by Immunohistochemistry

- Telomere Length Test
- DNAge™ Epigenetic Aging Clock
- EpiHealth
- DNAge® Test
- EpiLiver
- TeloYears + Advanced Ancestry Tests
- Epigenetic Age Analysis Version 2.0
- EpiAging
- EpiSocialpsych
- Targeted Seq. for DNA Methylation Analysis
- Telomere Length and Biological Age Testing
- EpiBreast

AGING ANALYTICS AGENCY

Biomarkers of Longevity

Distribution by **Operational Category**

AGING ANALYTICS AGENCY

Research Kit or Other Laboratory Practice Supplies

- ImmunoMAP v.1.0
- AngiogenesisMAP v.1.0
- CytokineMAP A
- MetabolicMAP v.1.0
- DiscoveryMAP v.3.3 Panel
- CytokineMAP B
- NeuroMAP v.1.0
- InflammationMAP v.1.0
- CardiovascularMAP v.3.0
- Explorer MAP v.1.0
- HumanMAP v.2.0
- LEGENDplex Human B Cell Panel
- LEGENDplex Human Th Cytokine Panel
- LEGENDplex Human CD8/NK Panel
- LEGENDScreen Human PE Kit
- Cell Regulation Panel
- Cardiovascular II Panel
- Organ Damage Panel
- Cardiovascular III Panel
- Immune Response Panel
- Metabolism Panel
- Neurology Panel
- Neuro Exploratory Panel
- Cardiometabolic Panel
- Oncology II Panel
- Oncology III Panel
- Inflammation Panel
- Phospho-H2AX (Ser139) cellular kit
- Human v3 miRNA Assay
- MiRXES ID3EAL miRNA Assay
- Senescence Detection Kit
- SPiDER-ßGal

Medical Test

- Aging Theranostic 1.0
- WellnessFX Premium
- Anti-Aging #4 Comprehensive Blood and Urine Test Panel
- InsideTracker Inner Age
- Healthy Aging Panel (Comprehensive)
- InsideTracker Ultimate Plan
- Female/Male Saliva Profile II - Test Kit for 6 Hormone Level Imbalances
- 10 Hormone Saliva Test Kit
- Adrenal Check
- Oxidative Stress Analysis 2.0
- NeuroGenomic™ Profile
- Comprehensive Adrenal Stress Profile
- Metabolic Analysis Profile (Organic Acids)
- ImmunoGenomic® Profile
- CardioGenomicPlus™ Profile
- Adrenal Stress Profile
- Advanced MethylDetox Profile + Thelomere Length
- Advanced MethylDetox Profile
- Immune-Frame
- aCGH RGCC
- PhysioAge Biomarkers of Aging Test
- Health + Ancestry Service
- Cytokine Panel
- Natural Killer Cell and Natural Killer T-Cell Panel
- CD57+ NK Cells, Peripheral Blood by Flow Cytometry
- CD21 (Dendritic Cell) by Immunohistochemistry
- B-Cell Memory and Naive Panel
- Cytokine Panel, TH1
- Regulatory T-Cell Panel
- Hepatic Function Panel
- CD4+ T-Cell Recent Thymic Emigrants
- Carnitine Panel
- Cytokine Panel

Informational Purpose Test or Platform

- Salivary Cytokine Panel
- DNAge™ Epigenetic Aging Clock
- Epigenetic Age Analysis Version 2.0
- DNAge® Test
- Targeted Seq. for DNA Methylation Analysis
- Genetic Age Test
- EpiLiver
- EpiBreast
- EpiHealth
- EpiAging
- EpiSocialpsych
- GlycanAge Test
- Viome Gut Intelligence™ Test
- Microba Insight™
- Gut Microbiota Biohacker
- smartGUT™ Microbiome Test
- Telomere Length and Biological Age Testing
- TeloYears + Advanced Ancestry Tests
- toxomiRTM biomarkers of toxicity
- thrombomiRTM biomarkers of platelet function
- Telomere Length Test
- osteomiRTM validated bone biomarkers

Epidemiological or Theoretical Panel Only

- Biomarker Panel
- OMIP-004: In-Depth Characterization of Human T Regulatory Cells.
- OMIP-007: Phenotypic Analysis of Human Natural Killer Cells.
- OMIP-027: Functional Analysis of Human Natural Killer Cells.
- OMIP-018: Chemokine Receptor Expression on Human T Helper Cells
- OMIP-039: Detection and analysis of human adaptive NKG2C+ natural killer cells.
- OMIP-029: Human NK-Cell Phenotypization.

Biomarkers Real-Time Assessment Technology

- AgeMeter
- Health Reviser Platform
- MEDIAGE™ Biological Age Measurement System
- AGE-Reader mu Test

AI Platform

- PhotoAgeClock
- Haut.AI Skin Health
- Aging.AI
- Young.AI
- CarePredict Platform
- Enlitic Platform
- Freenome Platform
- AI-Powered Radiology Assistant
- PathAI Platform
- Buoy Health Platform
- Tempus Platform
- BenevolentAI Platform
- KenSci Platform
- Digital Nutrition Platform
- Proscia Platform
- Ada Symptom Checker app
- Google's DeepMind Health AI Platform
- Blood Chemistry Calculator
- Better Therapeutics Platform
- Babylon Health Platform
- ICabonX Platform

Biomarkers of Longevity

Distribution by **Conditioning Stage**

AGING ANALYTICS AGENCY

Stage One: Research Use Only

- LEGENDplex Human Th Cytokine Panel
- LEGENDplex Human CD8/NK Panel
- LEGENDScreen Human PE Kit
- Freenome Platform
- ImmunoMAP v.1.0
- AngiogenesisMAP v.1.0
- CytokineMAP A
- MetabolicMAP v.1.0
- DiscoveryMAP v.3.3 Panel
- CytokineMAP B
- NeuroMAP v.1.0
- InflammationMAP v.1.0
- CardiovascularMAP v.3.0
- LEGENDplex Human B Cell Panel
- Salivary Cytokine Panel
- Explorer MAP v.1.0
- HumanMAP v.2.0
- Cell Regulation Panel
- Organ Damage Panel
- Cardiovascular II Panel
- Cardiovascular III Panel
- Tempus Platform
- Immune Response Panel
- Metabolism Panel
- Neurology Panel
- Oncology II Panel
- Oncology III Panel
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- Inflammation Panel
- Phospho-H2AX (Ser139) cellular kit
- Human v3 miRNA Assay
- Senescence Detection Kit
- MiRXES ID3EAL miRNA Assay
- SPiDER-βGal
- Proscia Platform
- BenevolentAI Platform
- Cytometry OMIP-004
- Cytometry OMIP-018
- Cytometry OMIP-039
- iCarbonX Platform
- Cytometry OMIP-027
- Cytometry OMIP-007
- Cytometry OMIP-029

Stage Two: Healthcare-Ready

- PhotoAgeClock
- Haut.AI Skin Health
- Aging.AI
- Young.AI
- Enlitic Platform
- Digital Nutrition Platform
- Salivary Cytokine Panel
- DNAge™ Epigenetic Aging Clock
- PathAI Platform
- Buoy Health Platform
- Epigenetic Age Analysis Version 2.0
- DNAge® Test
- KenSci Platform
- AI-Powered Radiology Assistant
- Targeted Seq. for DNA Methylation Analysis
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- EpiBreast
- EpiHealth
- Blood Chemistry Calculator
- EpiAging
- EpiSocialpsych
- GlycanAge Test
- TeloYears + Advanced Ancestry Tests
- Viome Gut Intelligence™ Test
- Microba Insight™
- Gut Microbiota Biohacker
- smartGUT™ Microbiome Test
- Telomere Length and Biological Age Testing
- thrombomiRTM biomarkers of platelet function
- Telomere Length Test

Stage Three: Approved for Clinical Use

- Aging Theranostic 1.0
- WellnessFX Premium
- InsideTracker Inner Age
- Anti-Aging #4 Comprehensive Blood and Urine Test Panel
- Healthy Aging Panel (Comprehensive)
- InsideTracker Ultimate Plan
- 10 Hormone Saliva Test Kit
- Adrenal Check
- Oxidative Stress Analysis 2.0
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- ImmunoGenomic® Profile
- CardioGenomicPlus™ Profile
- Advanced MethylDetox Profile
- Adrenal Stress Profile
- Advanced MethylDetox Profile + Thelomere Length
- aCGH RGCC
- PhysioAge Biomarkers of Aging Test
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- Babylon Health Platform
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- Natural Killer Cell and Natural Killer T-Cell Panel
- CD4+ T-Cell Recent Thymic Emigrants
- AgeMeter
- Cytokine Panel
- Hepatic Function Panel
- Ada Symptom Checker app

Biomarkers of Longevity

Distribution by **Amplitude Level**

AGING ANALYTICS AGENCY

Panels

InsideTracker Inner Age
InsideTracker Ultimate Plan
aCGH RGCC
RGCC Immune-Frame
Comprehensive Adrenal Stress Profile
B-Cell Memory and Naive Panel
Natural Killer Cell and Natural Killer T-Cell Panel
Health + Ancestry Service
Carnitine Panel
Cytokine Panel, TH1
Hepatic Function Panel
Regulatory T-Cell Panel
Cytokine Panel
Oxidative Stress Analysis 2.0
Adrenal Check
Adrenal Stress Profile
Advanced MethylDetox Profile
Advanced MethylDetox Profile + Thelomere Length
AGE-Reader mu Test
Female/Male Saliva Profile II - Test Kit for 6 Hormone Level Imbalances
Cytokine Panel
Healthy Aging Panel (Comprehensive)
biobank Biomarker Panel
WellnessFX Premium
Aging Theranostic 1.0
10 Hormone Saliva Test Kit
NeuroGenomic™ Profile
Metabolic Analysis Profile (Organic Acids)
Anti-Aging ₴4 Comprehensive Blood and Urine Test Panel
PhysioAge Biomarkers of Aging Test
CardioGenomic Plus Profile
ImmunoGenomic Profile
Metabolism Panel
Immune Response Panel
Cardiovascular II Panel
Cell Regulation Panel
Organ Damage Panel
Neurology Panel
Inflammation Panel
Cardiovascular III Panel
Neuro Exploratory Panel
Cardiometabolic Panel
Oncology III Panel
Oncology II Panel
HumanMAP v.2.0
MetabolicMAP v.1.0
CardiovascularMAP v.3.0
DiscoveryMAP v.3.3 Panel
AngiogenesisMAP v.1.0
NeuroMAP v.1.0
ImmunoMAP v.1.0
Explorer MAP v.1.0
InflammationMAP v.1.0
CytokineMAP B
CytokineMAP A
LEGENDplex Human CD8/NK Panel
LEGENDplex Human B Cell Panel
MiRXES ID3EAL miRNA Assay
Phospho-H2AX (Ser139) cellular kit
Senescence Detection Kit
SPIDER-βGal
OMIP-004
OMIP-018
OMIP-039
Salivary Cytokine Panel
LEGENDScreen Human PE Kit
LEGENDplex Human Th Cytokine Panel
OMIP-027
OMIP-007
OMIP-029
Human v3 miRNA Assay
smartGUT™ Microbiome Test
Genetic Age Test
Viome Gut Intelligence™ Test
Gut Microbiota Biohacker
toxomiRTM
biomarkers of toxicity
Microba Insight™
GlycanAge Test
osteomiRTM
validated bone biomarkers
thrombomiRTM
biomarkers of platelet function

Single Biomarker

CD4+ T-Cell Recent Thymic Emigrants
CD57+ NK Cells, Peripheral Blood by Flow Cytometry
CD21 (Dendritic Cell) by Immunohistochemistry
EpiBreast
Telomere Length Test
DNAge™ Epigenetic Aging Clock
DNAge® Test
EpiHealth
EpiSocialpsych
EpiLiver
TeloYears + Advanced Ancestry Tests
Epigenetic Age Analysis Version 2.0
EpiAging
Targeted Seq. for DNA Methylation Analysis
Telomere Length and Biological Age Testing

Digital Panel Platform

Babylon Health Platform
Centers for Age Control AgeMeter
CarePredict Platform
Ada Symptom Checker app
Health Reviser Platform
Blood Chemistry Calculator
AI-Powered Radiology Assistant
Google's DeepMind Health AI Platform
MEDIAGE™ Biological Age Measurement System
KenSci Platform
Enlitic Platform
Aging.AI
Young.AI
PathAI Platform
Buoy Health Platform
PhotoAgeClock
Haut.AI Skin Health
Digital Nutrition Platform
Proscia Platform
Freenome Platform
BenevolentAI Platform
Better Therapeutics Platform
Tempus Platform
ICabonX Platform

Baseline Amplitude Level

Maximum Amplitude Level

Deep Knowledge Group:
Scope of Activities

Deep Knowledge Group **Analytical Subsidiaries**

DEEP KNOWLEDGE ANALYTICS

Deep Knowledge Analytics

Deep Knowledge Analytics is a deep tech analytical agency using multidimensional algorithms to produce advanced industrial reports on DeepTech and frontier technologies. An online analytics platform with interactive visuals updated in real-time was released early this year.

DEEP KNOWLEDGE ANALYTICS *Pharma Division*

Pharma Division

The Pharma Division of Deep Knowledge Analytics specializes in the production of the most comprehensive analytical reports on the topics of Artificial Intelligence, Drug Discovery, Data Science and Digital Health within the broader Pharma Healthcare Industry and intersection of AI and Pharma.

DEEP KNOWLEDGE ANALYTICS *GovTech Division*

GovTech Division

The GovTech Division of Deep Knowledge Analytics focuses on producing sophisticated open-access and proprietary analytics the reveal factors driving the ongoing transformation of the global GovTech industry, main sectors to be changed, barriers to this process, and ways to overcome them.

AGING ANALYTICS AGENCY

Aging Analytics Agency

Aging Analytics Agency began producing reports before the industry emerged and it is exclusively focused on Longevity, Geroscience, AgeTech and Preventive Medicine. The company has been developing its methodology since 2015 and is the main source of market intelligence in the field.

Innovation Eye

Innovation Eye is a company providing market analytics and benchmark case studies. It has advanced tools for analysis and visualisation of Tech and innovation ecosystems. Its ultimate goal is to optimize the strategic agendas of corporations and governments seeking to optimise their Tech driven industries.

Aging Analytics Agency: **Producing Longevity Industry Reports Since 2013**

Aging Analytics Agency is the only specialized analytics agency in the world that focuses exclusively on the emerging Longevity Industry, Aging, Geroscience, P4 Medicine and AgeTech. Being recognized internationally as the premier analytics agency for advanced data analysis, industry reports and next-generation infographics on the topics of Aging and Longevity, also provides strategic consulting in the fields of Longevity and Economics of Aging.

Now in its 5th year, Aging Analytics Agency has been on the frontlines of Longevity Analytics since the inception of the industry.

Dmitry Kaminskiy, co-founder of Aging Analytics Agency, boldly predicted in 2014 that the Longevity Industry would see an inflection point in its development in 2017, becoming a recognized industry in the eyes of conservative investors, business analysts and top business media. This was at a time when investors and gero-scientists alike were highly skeptical of the industry's emergence within the next decade.

This prediction turned out to be true. 2017 witnessed an unprecedented rise in the number of Longevity-focused companies and investment deals, the emergence of half a dozen of geroscience-focused VC firms, coupled with widespread coverage of Longevity as a topic by mainstream media including The Economist, Financial Times and Bloomberg.

Since its establishment in 2013, Aging Analytics Agency has been systematically producing reports documenting the rise of Longevity Industry and Geroscience.

In 2014, Aging Analytics Agency successfully predicted the boom in Longevity Industry development and financing rounds of 2017, at a time when the vast majority of investors, business analysts, and even geroscientists believed that its emergence will only take place in the next decade. Its advantage over other analytics entities lays in its specific focus on the emerging Longevity Industry as well as P4 Medicine.

Aging Analytics Agency **Unique Approach**	The use of advanced infographics to distill complex industry landscapes into unified frameworks, enabling comprehension of pertinent data at a single glance.	The use of tangible, quantifiable, and proven metrics to conduct near-future industry forecasts, including Technology Readiness Levels (TRLs), to examine a given technology's market-readiness.	A strong focus on the convergence of multiple industries and technologies enabling the identification of indiscernible mega-trends and providing a bird-eye view of industry developments as a whole.

Uniquely Positioned to Provide
World-Class Longevity Analytics Reports and Services

Aging Analytics Agency not only forecast the true dawn of the Longevity Industry years before its mainstream recognition, but was willing to put its reputation at stake with a bold yet precise prediction when no one else saw it coming. Aging Analytics Agency's confidence stems from its reliance on tangible and quantitative predictive metrics, including the use of cross-disciplinary and synergetic analytical tools and frameworks to map the enormous diversity and complexity of the Longevity Industry.

The fruits of Aging Analytics Agency's labor significantly contributed to the exponential growth of Longevity as a topic in the mainstream, including its acceptance by business experts, media and even governments. The UK, for example, has listed Aging Population as one of its four grand challenges and launched a government-backed Healthy Aging Industrial Strategy Challenge Fund. Other governments have also launched similar strategic national development plans devoted to Longevity. Leading media brands, including TIME, Forbes, Bloomberg and others regularly publish Longevity-oriented cover stories. High-profile conferences on the subject of Longevity are more numerous than ever before.

LONGEVITY GOVERNANCE AND POLICY INITIATIVES

Metabesity and Longevity: USA Special Case Study. Joint Project with Targeting Metabesity 2019 Conference in Washington. Policy Proposal to the US Congress.

appg longevity

PROPOSAL

Proposal to the UK All Party Parliamentary Group on Longevity: "National Strategy for Five More Years of Healthy Life Expectancy in the UK.

WORLD HEALTH ORGANIZATION

PROPOSAL

Response to the World Health Organization's "Decade of Healthy Aging: 2020 – 2030 Draft Zero Action Plan"

Proposal to the United Nations on Optimization of International Longevity Policy and Governance

The company has been involved in charting the rise of the Longevity sphere since its inception and remained at the forefront throughout the past half decade. Thus, Aging Analytics Agency is uniquely positioned to produce both broadly-accessible reports and specialized case studies for specialized clientele including companies, investment firms, family offices and government agencies.

Many of these efforts are currently focused on the topics of **Longevity policy, politics** and **governance**, the formulation and development of **National Longevity Development Plans**, and targeted recommendations regarding decreasing the gap between life expectancy and **health-adjusted life expectancy** (HALE), developing various nation's Longevity industry to scale.

Open Access Analytical Reports by Aging Analytics Agency

Published / Q1 2019

Longevity Industry in California
Landscape Overview 2019

Longevity Industry in Singapore
Landscape Overview 2019

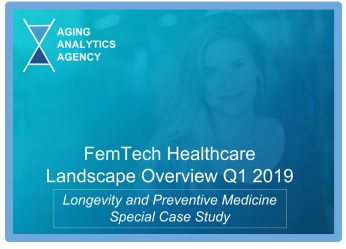
Longevity Industry in Israel
Landscape Overview 2019

Longevity Industry in UK
Landscape Overview 2019

Published / Q2 2019

Top-50 Women
Longevity Leaders

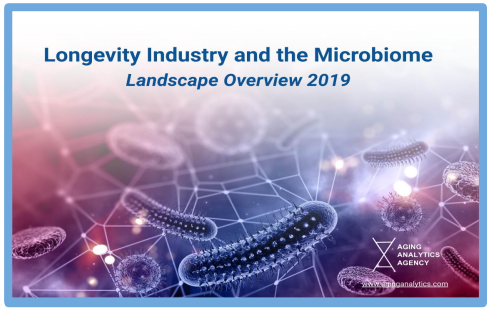
Top-100
Longevity Leaders



FemTech Healthcare
Landscape Overview Q1
2019

National Longevity
Development Plans: Global
Overview 2019
(First Edition)

Upcoming Analytical Reports by Aging Analytics Agency



Longevity Industry and the Microbiome
Landscape Overview 2019

Top-100 Supercentenarians

Metabesity & Longevity
USA Special Case Study

Longevity Industry in Switzerland
Landscape Overview 2019

Longevity Industry in Hong Kong
Landscape Overview 2019

Longevity Industry in Japan
Landscape Overview 2019

Introduction

Introduction

Aging Analytics Agency is currently developing a comprehensive, open-access report, Biomarkers of Longevity: Current state, Challenges and Opportunities Landscape Overview 2019, a special analytical case study that uses comprehensive analytical frameworks to rank and benchmark existing panels of biomarkers of aging, health 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.

The use of biomarkers is an indispensable component of industry analytics and assessment. It is the foundation upon which measurement of Healthy Longevity and the effectiveness of Longevity therapeutics is built. The report is designed as an in-depth review of the state of the art in biomarkers development to advise accurately the market, industry and public sectors when addressing the challenges related to our following conclusions and forecasts about the immediate future of the Biomarker and Longevity industries as a whole:

As the scope of P4 Medicine broadens, the number of biomarkers and measurement technologies and platforms will increase rapidly to the thousands in the coming years. This makes the implementation of P4 medicine impractical by current, manual means.

Aggregation of biomarkers of longevity and aging, rather than biomarkers of disease, and from healthy populations - among the young and the even younger, rather than bedside data from the hospital populations, will be part of everyday life due to the novel Digital Biomarkers capable of extracting truly massive amounts of clinical relevance data from a single patient through electronics.

That described shift will allow to move from the conventional therapeutic approach toward precision preventive medicine, and will also be the foundation for a unified theory of the root causes of aging and longevity; both providing a framework to intervene the process. Tech companies rather than healthcare companies will play the leading role in this process.

The use of AI will give sense to this thumping amount of data, and it will allow the development of surely multiple optimal panels of aging biomarkers as well as other health biomarkers (digital and non-digital) for analysis of each person's outcomes, and for orchestrating extremely personalized therapeutic interventions in response to fluctuations in those biomarkers. As the number of data points increases, it becomes not only optimal, but strictly necessary to use AI and big data analysis in not only the longevity industry, but in the health industry as a whole.

Introduction

The report is 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 action plans and strategies, providing specialized guidance for business and investment core decisions. It will deliver:

- **A "most comprehensive" list of single biomarkers of aging and Panels, their advantages and strengths, disadvantages and weaknesses, and future perspectives, challenges and opportunities with a focus on technologies currently used for assessment;**
- **Concrete analysis of recent novel biomarkers of aging just entering R&D processes today, emerging tools, and novel assay platforms awaiting approval or standardization for clinical implementation, one step away of being market-ready within the next several years;**
- **Highlights respecting why AI platforms will come to be a necessary and indispensable component of Longevity biomarker discovery, research and development;**
- **Overview of different categories of panels, whether for Research Use Only or Approved for Clinical Use;**
- **Conclusions and practical recommendations regarding the Most Comprehensive Panels and the Most Viable (Minimum Required) Panels for immediate implementation, either in biomedical research, therapy development, P4 medicine and clinical practice, emphasizing the relative and absolute usefulness of these Panels for precision measurement of biological age and enhanced assessments of health status, age-related diseases, geriatric syndromes, and Longevity.**

The parties with early access to this report will gain deep expertise on how they can optimize their development and implementation strategies, and how to analyze the technological and scientific backgrounds and prospects of the Longevity industry in order to deliver sophisticated action plans aimed for remaining at the forefront in the broad and changing field of healthcare.

Biomarkers for Paradigm Shift from Treatment to Prevention

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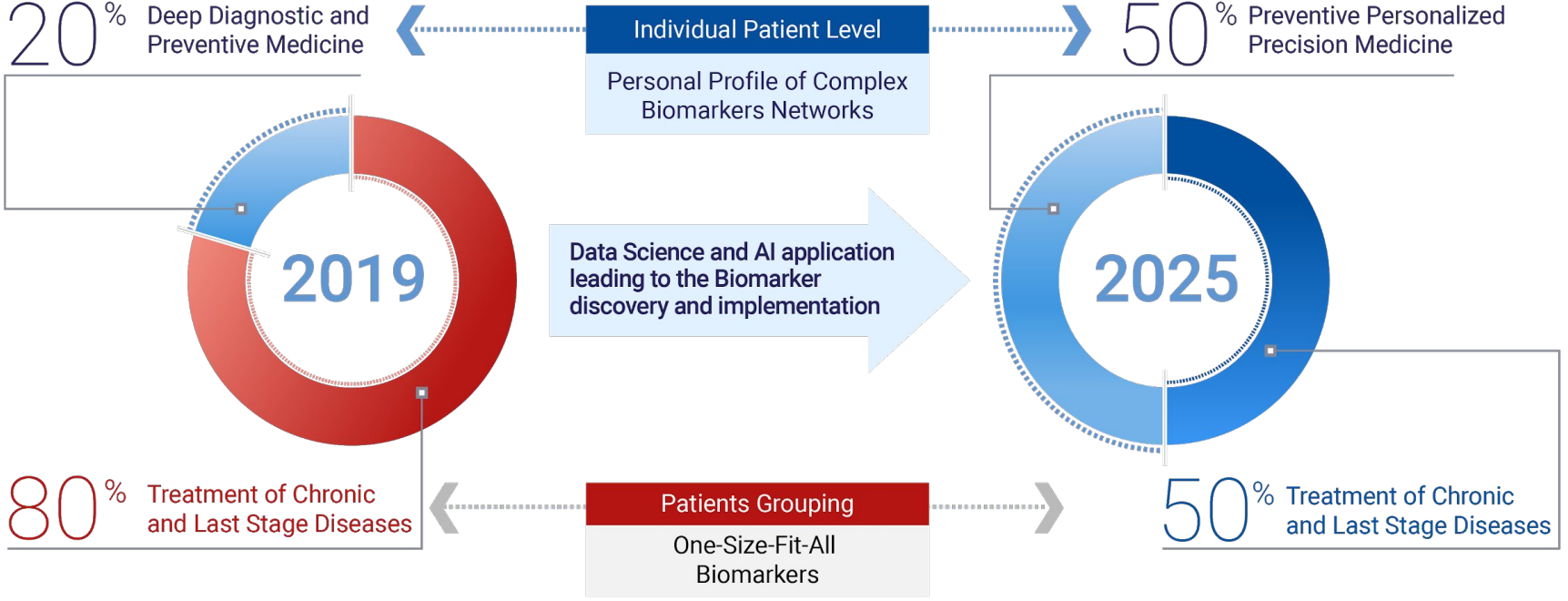
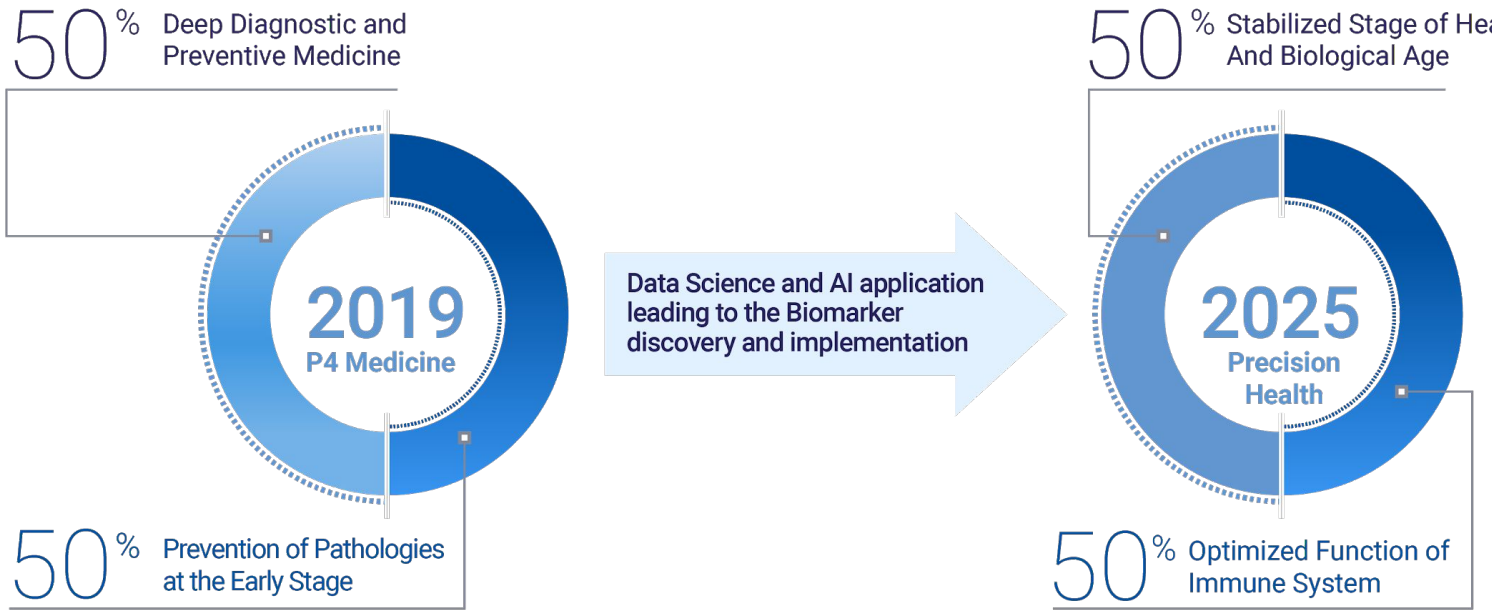


Jamie Metzl for Longevity.Technology: "First, we're increasingly understanding the biomarkers of aging. And that is giving us a language of measurement. We can assess with more precision whether certain interventions are working or not working. With the new tools of AI and machine learning we're really seeing is a super convergence of different technologies that are all pushing forward, including the science of human Longevity."

Biomarkers for Paradigm Shift from P4 Medicine to Precision Health

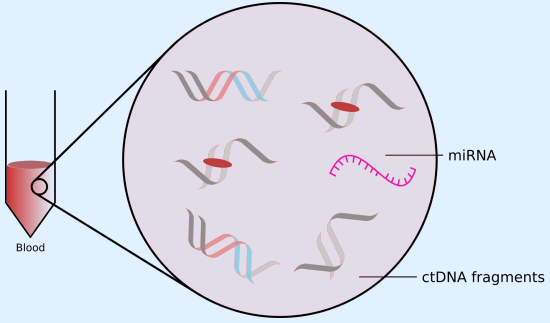
AGING ANALYTICS AGENCY



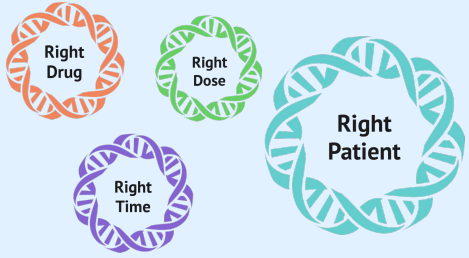
Since 2013, Deep Learning systems have surpassed human performance in multiple applications, such as face and image recognition. Predictors of chronological age, and biological age - or functional age-, are rapidly gaining popularity and with this a deep outburst of research and development is awakened, both in the scientific and industrial spheres. A new market is brewing. AI has shown that it is possible to overcome the best human ophthalmologists or radiologists, the best conventional predictors of complex pathologies such as Parkinson's and Alzheimer's have been surpassed. And in this framework, AI-driven biomedical research and development efforts are now already facing aging.

Introduction to 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. Regarding health related activities:

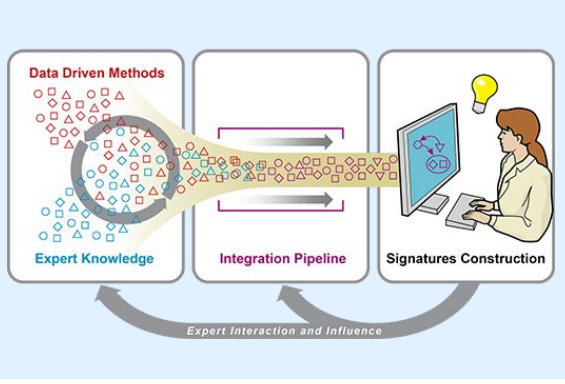


In **biomedical research** and **clinical practice**, biomarkers include measurements that suggest the etiology of, susceptibility to, activity of, or progress of a disease. The use of biomarkers in basic and clinical research as well as in clinical practice has become so commonplace that their presence 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 becomes 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.

Increased knowledge around the human genome and other omics, and correlations with disease risks and progression are expected to shift the current biomarker focus. Drug companies have been increasing their investment into exploratory biomarkers that focus on areas such as infectious diseases, central nervous system (CNS) disease conditions and cardiovascular diseases to broaden their overall biomarker research and development strategies. For example, CNS disease conditions such as schizophrenia, Parkinson's and Alzheimer's are finding initial success in biomarker identification for targeted therapies.



Introduction to Biomarkers. Conventional Classification Frameworks

For practical purposes, single biomarkers and biomarker panels used in the setting of biomedical research, drug discovery and development, and clinical practice are often classified following any of the criteria outlined below:

- **Clinical Outlook.** In relation to clinical specialties, to organ systems and related vital functions, and to subordinated diseases of each one. We find biomarkers for oncology profiling, cardiology and hematology profiling, neurology profiling, endocrinology, infectious diseases, immunology, and so forth. Due to the low degree of specificity, here we usually find large biomarker panels and not single biomarkers.
- **Disease and Conditions Outlook.** Within each clinical specialty or often overlapping a number of them, the set of biomarkers that make up the profile of a pathology or set of related pathologies. These categories are usually subsets of each one in the previous criterion, also using panels much more often than single biomarkers.
- **Functional and Structural Outlook.** Based on its association with specific functional and structural variables, either physical, anatomical, histological or physiological. For example, biomarkers for locomotor function, or for strength, balance, bone density, body impedance or waist circumference, in this case all closely interconnected parameters. This approach is usually subordinate to the previous two. Due to its higher degree of specificity, it usually allows the use of single biomarkers or small panels, although large panels are more descriptive.
- **Source Outlook.** By the source of the biological material or data, and its processing methodology. The clinical evaluation usually addresses a small amount of biomarkers related to one or a few conditions, or to the general state of health. A broad examination of the biomarker network provided by each test could allow the extraction of a large amount of data about health status.
- **Focus Level Outlook.** Based on the focus level, or the associated diagnostic or therapeutic depth, biomarkers can be divided by the domain to which they belong on the organismic scale.There are six categories or levels, Biochemistry, Genomic, Proteins and Cell Signalling, Cellular, Tissue and Organ markers, each one correlated with a particular set of evaluations, potential interventions, and an order of physical magnitude. Thus, Organ biomarkers are related to Regenerative medicine, and Biochemical ones include lipid-, glyc- and metabolomics among others.
- **Omic Outlook.** In relation to the *-omic* field to which they belong, what will determine the types of technologies and evaluation methods.
- **Application Outlook.** More typical of the market analysis, according to the activities in which biomarkers are applied, or 'what are they used for'.
- **Type Outlook.** Indispensable. Classification according to characteristics of its operational definition, or 'how are they used for'.

Biomarker Conventional Classification Frameworks

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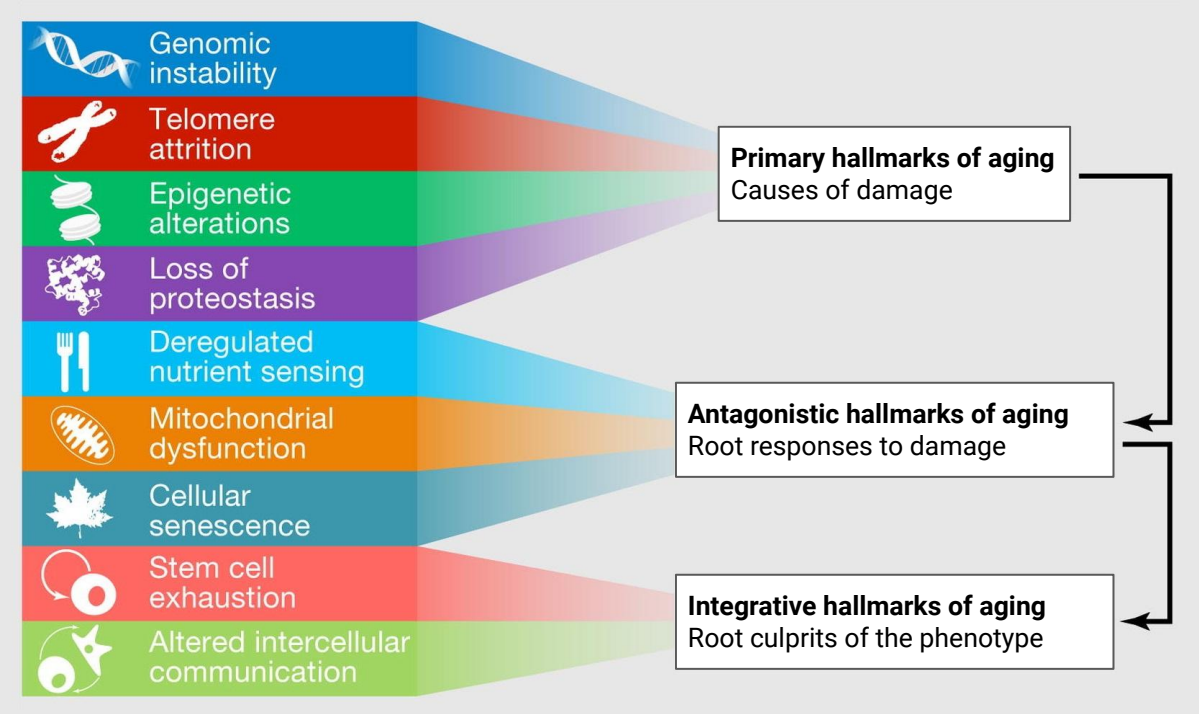
Clinical Outlook		Diseases and Conditions Outlook		Functional and Structural Outlook	Source Outlook	Focus Level Outlook	Omic Outlook		Application Outlook	Type Outlook	Age Mechanism Outlook
		Osteoporosis	Arthritis						Drug Discovery and Development		
		COPD	Sarcopenia						Drug Formulation		
Biological Age measurement	Ophthalmology	Aging-associated Metabolic Syndrome	Osteopenia						Preclinical Trials		Genomic Instability
Alcohol/drug treatment	Gastroenterology	Type II Diabetes	Obesity						Clinical Trials		Telomere Attrition
Oncology	Orthopaedics	Cancer	Alzheimer's Disease	Locomotor function; Dexterity					Diagnostic Development		Epigenetic Alterations
Cardiology	Hematology	Amyotrophic Lateral Sclerosis	Parkinson's Disease	Bone density; Bone mass hip					Diagnostic	Efficacy - *Pharmacodynamic*	Loss of Proteostasis
Neurology	Rheumatology	Hypertension	Cerebrovascular Disease	Muscle mass; Body impedance; Abdominal fat	Digital biomarkers + AI	Biochemistry level	Genomics	Transcriptomics	Disease Risk Assessment	Efficacy - *Predictive*	Deregulated Nutrient Sensing
Endocrinology	Sleep disorders	Atherosclerosis	Mild Cognitive Impairment	Blood pressure; Lipid profile; Glycated Hb	Human Biomonitoring	Genomic level	Epigenomics	Foodomics	Screening	Efficacy - *Prognostic*	Mitochondrial Dysfunction
Maternal-Fetal medicine	Urogynecology	Cardiovascular Disease	Dementia	Lung capacities; Transpulmonary pressure	Imaging	Proteins and Cell Signalling level	Metabolomics	Nutritional genomics	P4 Medicine	Efficacy - *Surrogate and Diagnostic*	Cellular Senescence
Infectious diseases	Dentistry	Coronary Artery Disease	Multiple Sclerosis	Processing speed; Working memory; Visual memory	Laboratory procedures (Blood, Saliva, Biopsy)	Cellular level	Proteomics	Pharmaco-genomics	Regenerative Medicine	Validation	Stem Cell Exhaustion
Dermatology	Otolaryngology	Deep Vein Thrombosis	Coordination impairment	Endocrine profile; HPA axis	Pedigree and Family History	Tissue level	Lipidomics	Pharmaco-microbiomics	Research	Safety	Altered Intercellular Communication
Allergology	Immunology	Blindness	Age-related Macular Degeneration	Chronic inflammatory status	Routine and Comprehensive Physicals	Organs level	Glycomics	Toxico-genomics			

Special mention apart, biomarkers in pharmaceutical industry research and development are predominantly described based on a **Type Outlook** classification, the most widely used criterion; that is, as validation, safety and efficacy biomarkers, and likewise also as surrogate and diagnostic, prognostic, predictive, and pharmacodynamic biomarkers, all categories that are not mutually exclusive since specific clinical setting can determine how the biomarker is used and interpreted. In the particular sphere of aging, age-related diseases and geriatric syndromes, biomarkers are usually classified according to an **Aging Mechanism Outlook:** by the root causes and the mechanisms or phenomena triggered by these causes; for instance, *loss of proteostasis* triggers *inflammaging* mechanisms, although this is not the single cause of age-related low grade inflammation.

Biomarker Conventional Classification Frameworks

AGING ANALYTICS AGENCY



Aging Mechanism Outlook. The proposed nine hallmarks of aging are grouped into three categories. Those hallmarks considered to be the primary causes of cellular damage. Those considered to be part of compensatory or antagonistic responses to the damage. These responses initially mitigate the damage, but eventually, if chronic or exacerbated, they become deleterious themselves. Integrative hallmarks that are the end result of the previous two groups of hallmarks and are ultimately responsible for the functional decline associated with aging.

Sources Image: López-Otín C., et al. The hallmarks of aging. *2013*.

Techniques of Biomarker Analysis

In the last two decades, the use of biomarkers in biomedical research and drug discovery and development has seen rapid growth as a result of the advancement of laboratory techniques and bioanalytical assays, fundamentally:

- **Ligand-Binding Assays (LBA), such as Enzyme-Linked ImmunoSorbent Assay (ELISA);**
- **Quantitative Polymerase Chain Reaction (qPCR);**
- **Mass Spectrometry (MS)-based technologies.**

These and other technologies of biochemical laboratory, analytical chemistry and biophysics, have allowed the identification and characterization of innumerable genetic, molecular and cellular biomarkers, as well as their direct relationship with mechanism of disease or processes substantially downstream from the primary disease processes. Despite this, due to economic viability limitations, regulatory or standardization issues, high technical difficulty or time consumption, excessive specialization skills requirements, or lack of clinical certainty about usefulness in health promotion, prevention, diagnosis, treatment, or prognosis, many technologies, techniques and biomarkers have been restricted to Research Use Only (RUO), not taking place the transition or adaptation for Approved Clinical Use (ACU) or taking place in a very slow and limited way.

Because of the substantial risk of adversely affecting the public health if a biomarker is falsely accepted as a surrogate endpoint, robust scientific evidence is needed to justify qualification of a biomarker for that use. There have been numerous biomarkers that represented plausible surrogate endpoints, but when tested in outcome trails these have failed to predict the expected clinical manifestation. Qualification of a biomarker as a surrogate endpoint will inevitably occur far less frequently than qualification of a biomarker for other uses. In this sense, to shorten the translation delay from RUO to ACU, and for a deep impact on population health care as well as in the field of research and development, it is essential to move towards the definitive establishment of digital health and P4 Medicine.

The disruptive impact of P4 Medicine is a consequence of the emergence of now well seated technologies of Data Science and AI making possible the mapping and construction of biomarker networks, giving birth to a new market-ready health care paradigm: deep precision care along with daily real-time digital monitoring to continuously adjust and set up the optimal state of health, and early stage prevention treatment.

What are Biomarkers of Aging?

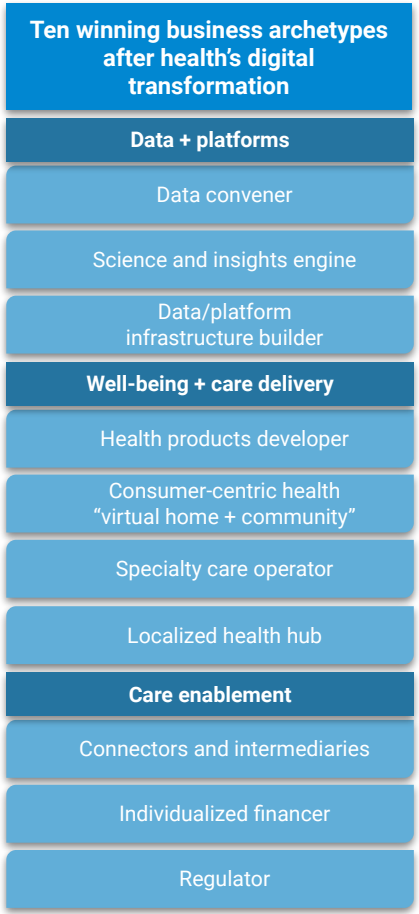
Aging is a major risk factor for most chronic diseases and functional impairments. Within a homogeneous age sample there is considerable variation in the extent of disease and functional impairment risk, revealing a need for valid biomarkers to aid in characterizing complex aging processes. The identification of biomarkers is further complicated by the diversity of biological living situations, lifestyle activities and medical treatments.

Thus, there has been no identification of a single biomarker or gold standard tool that can successfully monitor healthy aging, or perhaps not until the recent development of Horvath's Epigenetic Clock and Glycomic Biomarkers.

How do we know when a biomarker is a **Biomarker of Aging**? It depends on how it is sourced. The current approach to biomarkers is to take them from people at various stages of a disease's known progress, which in practice means sourcing them from hospital patients. Isolating biomarkers of aging, however, means collecting data which marks the difference between healthy people only, e.g. between the young and even younger, with no traces of any officially recognised diseases.

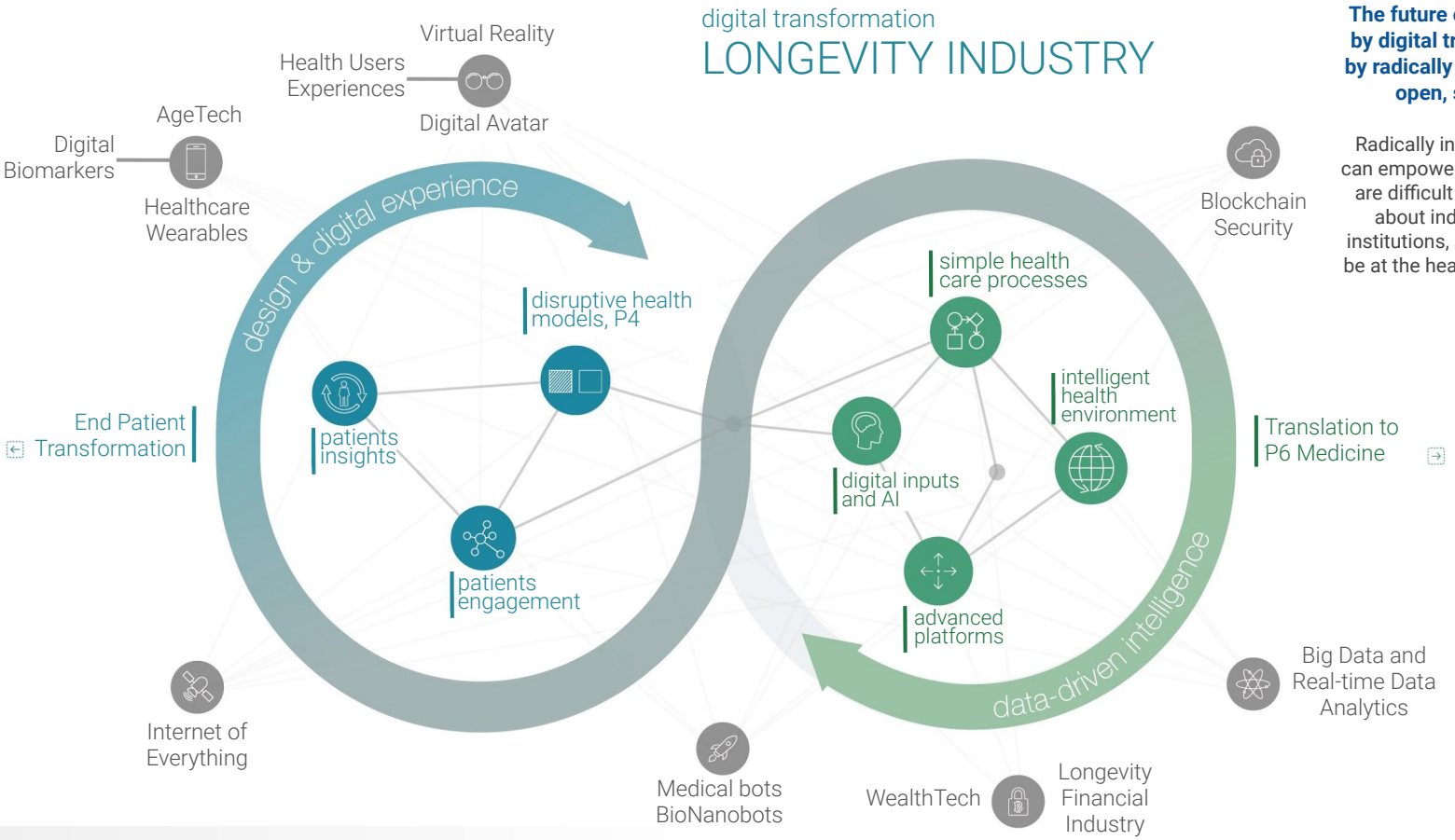
A special focus of Aging Analytics Agency, is the use and recommendation of AI for the development of an optimal Panel of Biomarkers of Aging – a specific niche where the implementation is lagging behind the science. This is one of the most important diagnostic services that could be offered, and yet it does not receive the attention it deserves compared to the amount of tangible benefits it can deliver.

The diagnostic technologies of the future should be anchored to Panels of Aging Biomarkers digitally obtained. This will enable the current state of health of each patient to be continually and precisely monitored, allowing the effectiveness of interventions and micro-adjustments to interventions to be continuously assessed in detail, enabling an unprecedented degree of precision and prevention in biomedicine, and an unprecedented degree of prescience in biomedical research. **This, in a nutshell is the nature of the aforementioned digital transformation of the Longevity Industry.**



Sources Image: *Data from* Deloitte.

Digital Transformation of the Health and Longevity Industry



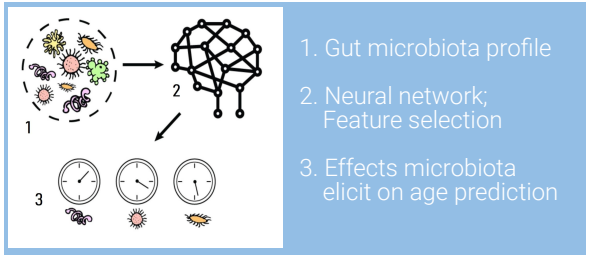
The future of health will be driven by digital transformation enabled by radically interoperable data and open, secure platforms.

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.

Sources Image: *Modified from* everis.

What are Biomarkers of Aging?

Biomarkers of Aging are biomarkers that could predict functional capacity at some later age better than will chronological age. Stated another way, biomarkers of aging would give the true Biological Age, which may be different from the Chronological Age.



Within this frame, **Biological Age** is intended as a synthetic index constituted by a single marker or the combination of few biological markers which, alone or integrated with functional markers, not only correlates with chronological age but is/are capable of identifying individuals "younger" or "older" than their chronological age in the same demographic cohorts; i.e., with a different health status, globally or in relation to a particular vital function or organ system, allowing this index to accurately predict future health status and functional capacity.

Validated Biomarkers of Aging would allow for testing interventions to extend lifespan, because changes in the biomarkers would be observable throughout the lifespan of the organism. Although maximum lifespan would be a means of validating biomarkers of aging, it would not be a practical means for long-lived species such as humans because longitudinal studies would take far too much time.

Ideally, biomarkers of aging should:

- Assay the biological process of aging itself and not only the predisposition to disease, since the vast majority of the aging process occurs without pathological manifestation;
- Cause a minimal amount of trauma to assay in the organism, thus enabling continuous measurement and analysis that do not cause morphofunctional damage, which ultimately results in aging;
- Be measurable with high reproducibility during extremely short intervals compared to the lifespan of the organism.

With such biomarkers, it should be possible to obtain Trajectories of Aging, where the "accelerated" ones would predict unhealthy aging and diseases, while the "decelerated" ones would be associated with healthy aging and longevity. The possibility to draw Trajectories of Aging is a fascinating, far-reaching perspective, especially in consideration of the long incubation preclinical period that characterizes most of the major age-related chronic diseases, being also considered the critical time window for effective treatments. Biomarkers of Biological Age could greatly contribute to identify the subjects characterized by higher risk to develop overt clinical diseases who would have a major benefit from tailored preventive treatments.

AI-Driven Development of Biomarker Panels of Aging

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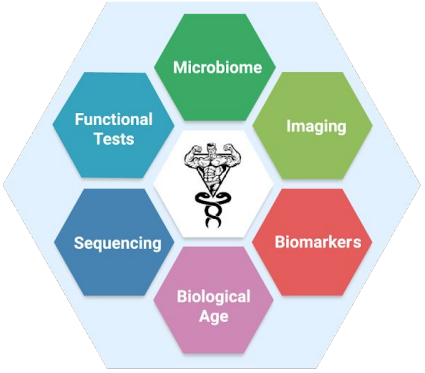

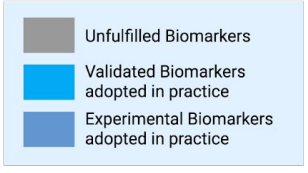

Biomarker panel

Artificial Intelligence will use Digital Biomarkers to reality-check the proposed longevity therapies and filter out inappropriate or impractical biomarkers from those effective.

Precision Prevention, Diagnosis, Treatment and Prognosis

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As the Precision Health industry is grown and developed to scale, we will see an increasing emphasis on the creation and validation of a wide diversity of Biomarkers of Aging come into use, which will enable the extension of healthspan and the maintenance of optimal health for the majority of citizens' lifespans via continuous, AI-empowered monitoring of fluctuations in personalized Biomarkers of Aging.

P4 Medicine will be the central platform giving effective usefulness to Aging Biomarkers for healthcare. It is not possible to think about extension of life expectancy and healthspan without P4 Medicine.

A patient may see that their biological age is 36 in 2021 — younger than a couple of years before, and younger than their chronological age of 37.

Gathering Aging Biomarkers means collecting data which marks the difference between healthy people only, e.g. between the young and even younger, with no traces of any officially recognised diseases. The continuous monitoring of small changes in such biomarkers, and the continuous and commensurate micro-adjustment of treatments in response, allows for some de facto reversal of biological age.

What are Biomarkers of Aging?

Aging Biomarkers already exist, but they are going through a period of discussion and validation. A major biomedical aim of these biomarkers today is to identify the subjects at higher risk for each specific age-related disease and syndrome at very early stage; the challenge of precision preventive medicine.

At present, the combination of last generation effective biomarkers, capable of assessing the deep biological age, with some classical and innovative biochemical and functional disease-specific ones, represents the best strategy to identify **Disease-Specific Aging Trajectories** in each individual. This is the core conclusion and recommendation of our analytical assessment.

Within this perspective, particular attention has to be devoted to the epigenetics, but also the genetics of each individual which is the complex result of the interaction between nuclear and mitochondrial genetics (stable with the exception of somatic mutations) and microbiomes' genetics (malleable and adaptive to the environment), focusing on Gut Microbiota Biomarkers for its capability to be modified by basic habits such as nutrition.

In this sense, we predict that it will be useful enough to combine the above mentioned integrated biomarkers' assessment (particularly the Horvath's Epigenetic Clock with some widely used and conventional routine biomarkers) with established and new genetic risk factors for Aging-Related Diseases, taking into account some criticalities related to population genetics and demographic birth cohorts.

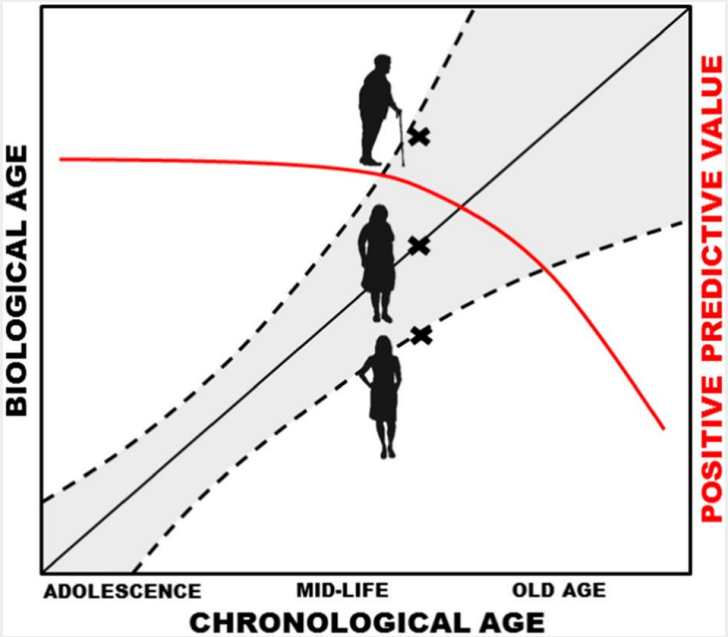
It must be mentioned; although a number of promising Aging Biomarkers candidates have been proposed in the last years, to date there are no clinically validated ones. There are three disruptive and non mutually exclusive categories of last generation Biomarkers of Biological Age that have revolutionized the sector due to its high correlation with chronological age and trajectories of age-related diseases, being of mandatory mention:

- **DNA Methylation Biomarkers**, especially the Horvath's Clock,
- **Glycomic Biomarkers**, and
- **Gut Microbiota Biomarkers**, also called Microbiome Biomarkers.

All of them have presence in the market as informational purpose tests provided by certain companies, but not clinical tests. And each one is up to the challenge of establishing itself as a self-sufficient metric of Biological Age; particularly the first mention. The integration of any of these into a Biomarker Panel would not only serve as a reference to evaluate the implication of the remaining, traditional ones like a Lipid Profile, in aging decline; such a far-reaching and proactive decision would also accelerate the process of their clinical validation both to measure Biological Age and for the evaluation of specific diseases in any other given context.

Biomarkers of Aging

In summary, research on healthy aging and longevity encompasses the biological processes contributing to aging per se; the socio-economic and environmental exposures across life which modulate aging and the risk of age-related frailty, disability and disease; and the development of interventions which may modulate the aging trajectory.



Such research needs measures of Biological Age at the individual level which, in addition to Chronological Age, can characterise and quantify important functions which are subject to decline at faster, or slower, rates during individual human aging.

Biomarkers of healthy aging could be used as surrogate endpoints or outcome measures in trials of interventions designed to extend healthspan, and public health-related population surveys would benefit from reliable, readily-measured indices of healthy aging. Nevertheless, there is no criterion reference for assessing healthy aging and this creates difficulties when conducting and comparing research on aging across studies. Herein the need for Maximally Actionable Aging Biomarkers Panels.

Healthy aging and wellbeing are common goals in all modern societies. The demographic shift towards higher proportions of older people within the population in practically all countries worldwide, and the recognition that much of the costs of health and social care in economically-developed countries is densely concentrated in the last decade of life, have sharpened globally the research focus on aging and longevity.

The concept of biological age predictors. A biological age predictor could be defined as a biomarker correlated with chronological age (black line), which brings additive information in the risk assessments for age-related conditions on top of chronological age. Hence, adult individuals of the same chronological age could possess different risks for age-associated diseases as judged from their biological ages (x's in figure). Usually, the positive predictive value (red line) of a biological age predictor decreases from mid-life and onwards due to the increased biological heterogeneity at old age (confidence interval described by dashed lines increases at old age).

Sources Image: Juulia Jylhävä, et al. Biological Age Predictors. *2017.*

The Need for Maximally Actionable Biomarkers of Aging

It is important in technology never to let the perfect be the enemy of good, especially when the technology is of great humanitarian significance. Aging Analytics Agency has observed a tendency among governments and political strategic bodies to make the error of assuming that because the current scientific quest for ever more precise biomarkers is not slowing down, that we don't yet have a set of biomarkers precise enough and actionable enough to take immediate action.

It is important therefore to develop and promote the widespread use of a panel of biomarkers which are not only comprehensive but also immediately actionable. A panel of less precise but easily implementable biomarkers of aging would be much better than an extremely precise and comprehensive panel of biomarkers of aging that is too hard or expensive to translate easily into widespread practical use across nations. As an example of minimum viable biomarkers, consider that a set of of aging biomarkers was developed recently which is based on Deep Learning analysis of standard blood biomarkers, which is less accurate than the most precise available biomarkers of aging (DNA Methylation clocks), but which is nonetheless good enough, and can be implemented by any researcher, doctor and clinician that has access to routine blood tests.

As a further example, consider that biomarkers of aging have been constructed using Deep Learning-based analysis of photographs of mice, which could quite easily be extended to humans. Their accuracy alone is not enough to make them a research priority, but the increasing video capabilities of smart-phones means that these rapid development of photographic biomarkers of aging (e.g. of the face or the eye) could now be a very actionable area of research whose practical level of precision and accuracy will develop quite rapidly in coming years.

However, the use of AI in R&D is lagging behind in its application to geroscience. While there is a small handful of companies that are working at this frontier, the overall proportion in comparison to the total size of the Longevity industry is still quite small. Deep Knowledge Ventures has been identifying and supporting companies working on the frontlines of AI for Longevity since 2014, when it provided the seed funding for Insilico Medicine, now a leader in the application of AI for Longevity research, drug discovery and biomarker development. An MVP panel of biomarkers will make the biotech sector of Longevity much more lean, and dynamic. It will allow for a more rapid assessment period, which in turn will allow for a rapid succession of experiments with microdoses of different treatment and drugs.

What are Biomarkers of Aging?

It is impossible to determine whether biotechnologies for Longevity have been successful **if we cannot tell how advanced the aging process is in any given individual**; but at the same time the latter will not be feasible until successfully achieving **High Actionability Panels** that allow to evaluate the aging process in broad healthy and less healthy differentiated ranges of the population spectrum. From the above the following two notions emerge.

- It will be impossible to make concrete claims regarding global progress in health biotechnology, and in P4 Medicine in particular, without an agreed and accessible panel of biomarkers as a tool to standardize results.
- These biomedical markers, measurable indicators of the severity or presence of some disease state, are able to serve as the basis for building standard metrics for government programs and cost-effective healthcare policies, clinical implementations, and industrial output in global Longevity Industry.

Biomarkers of aging can be used to predict the biological age, which reflects the state of health, via statistics and machine learning algorithms. A single class of biomarkers, which is intrinsically a matrix of features, can be used in the prediction. DNA methylation was used to predict age with an error of about 3.6 years using 8,000 samples. 3D facial images have also been used to predict age with a mean deviation of 6 years. Integration of multiple biomarkers can be even more powerful.

Given the complex nature of the aging process, the biomarkers of aging are multilayered and multifaceted. Combined and integrated by AI and machine learning techniques, reliable panels of biomarkers of aging will have major and tremendous potential to improve human health in aging societies. Identifying and using biomarkers of aging organized in an objective and solidly founded panel to improve human health, prevent age-associated diseases, and extend healthy life span are now facilitated by this fast-growing AI-driven capacity for multilevel cross-sectional and longitudinal data acquisition, storage, and analysis, particularly for data related to general human populations.

Is in this sense that Biomarkers are an essential factor in Aging Analytics Agency's strategic agenda, which includes recommendations for the establishment of AI centres in the United Kingdom, the indispensable medium to nail down the implementation of P4 Medicine and also to guarantee competitiveness in the new global health market, in the same way that highly specialized advice for the success of longevity-related government initiatives worldwide.

Sources: Xian Xia, et al. Molecular and phenotypic biomarkers of aging. *2017.*

The Need for Maximally Actionable Biomarkers of Aging

It is important in technology never to let the perfect be the enemy of good, especially when the technology is of great humanitarian significance.

In the early 2000s, enthusiastic proponents of the application of Regenerative Medicine to aging were urging governments, entrepreneurs and thought-leaders to make this a priority. They argued that technology was ahead of the science and the funding, and that while a great deal remains to be discovered about the mechanisms of aging, we already know enough to optimize the existing toolkit of Regenerative Medicine to address the damage of aging, which is already thoroughly researched. And thus, shift occurred out of this paradigm and the field of Rejuvenation Biotechnology arose.

Now once again, the technology is ahead of the science, the funding, and the political leadership. And, once again, a paradigm shift is due.

Presently the necessary biotechnologies for the implementation of P4 Medicine technologies and therapies are already in place. What is needed now is Big Data analytics to develop optimal Panels of Biomarkers of aging and to determine how to optimize their implementation. Thus, this is not a biotechnology problem, but a data mining, analysis and management problem. In many countries, to various degrees, data mining, analysis and management problem is a question of political coordination. In that way, there is a risk that governments and governmental or political strategic bodies may make one or both of the following errors:

- They might assume that missing bridge on the road to **HALE-extending P4 Medicine** is still biotech progress, rather than a data analysis and management problem; i.e., an AI and computational problem;
- They might assume that current scientific quest for ever more precise Biomarkers is not slowing down because we don't have yet a set of Aging Biomarkers sufficiently actionable and precise, in order to take immediate action.

As such government strategic bodies therefore risk limiting their strategic ambitions with regard to time frames. For example, in the United Kingdom, Theresa May's government has announced a commitment to adding 5 extra years on the nation's HALE by 2035, whereas Aging Analytic Agency has subsequently advised the UK's newly formed APPG for Longevity that a much more relevant timeline would be 2025, provided **actionable biomarkers with sufficient accuracy are utilized**. This aspiration better reflects real current rate and state of scientific and technological innovation.

The Need for Maximally Actionable Biomarkers of Aging

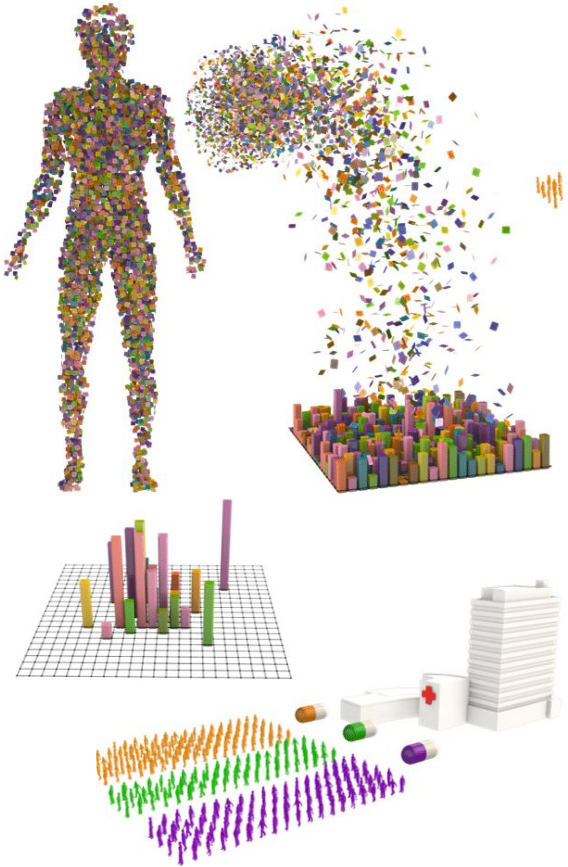
Aging Analytics Agency is recommending that government place a strategic emphasis not on the best Biomarkers of Aging, but on a Panel of Biomarkers that has the highest ratio of comprehensiveness to actionability and implementability.

Having a panel of less precise but highly implementable Biomarkers of Aging close at hand is much better than having an extremely precise and comprehensive panel of biomarkers that is too hard or expensive to translate easily into widespread practical use across nations, **as the beneficiaries of earlier action are likelier to stand a chance of living long enough to subsequently benefit from more advanced applications** based on more precise, more comprehensive biomarkers.

The past few years have seen a lot of progress in the development of Biomarkers of Aging that are not as precise as the current leading methods, but that are precise enough, and most importantly, extremely easy to implement in practice -in particular, those based on *Deep-Learning* and *AI-driven* analysis of routine blood tests, and of photographs. These are highly viable Biomarker Panels.

Consider that set of Aging Biomarkers developed recently, based on Deep Learning analysis of standard blood biomarkers; while less accurate than the most precise available Aging Biomarker, DNA Methylation Clocks, is nonetheless good enough and can be performed by any researcher, doctor and clinician that has access to routine blood tests.

The **increasing video capabilities of smart-phones means that these rapid developments in Imaging Biomarkers of Aging** (for any physical or behavioral trait correlated with biological age) can now be a very actionable area of research whose practical level of precision and accuracy will develop quite quickly in coming years.



Sources Image: Olink. From protein biomarker discovery to precision medicine

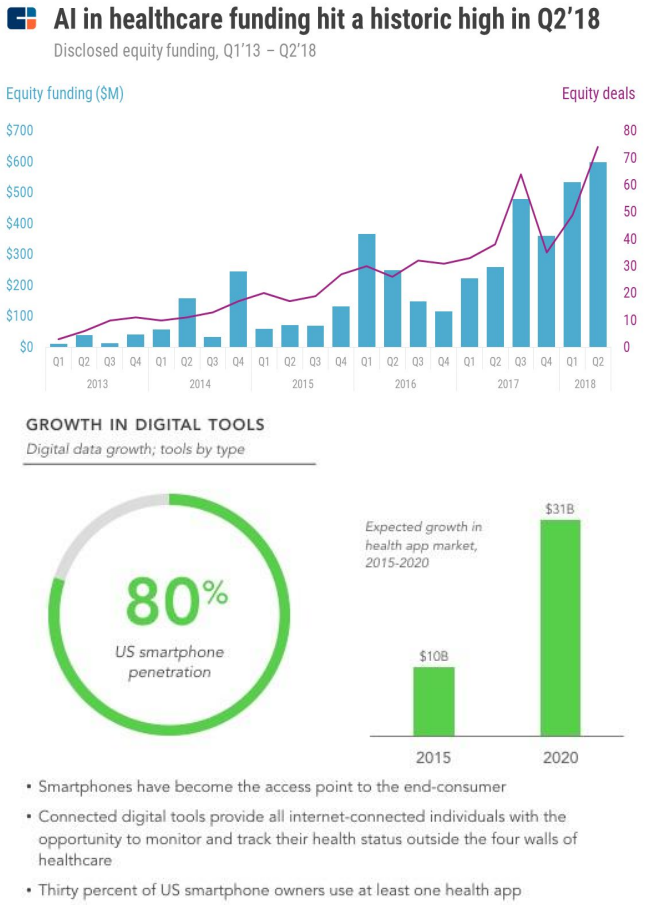
The Need for Maximally Actionable Biomarkers of Aging.

It should not be assumed that the use of Artificial Intelligence is widely embedded into biogerontology and geroscience. AI in R&D is lagging behind in its application to the Longevity industry. While there is a small handful of companies that are working at this frontier, the overall proportion in comparison to the total size of the Longevity industry is still quite small.

Deep Knowledge Ventures has been identifying and supporting companies working on the frontlines of AI for Longevity since 2014, when it provided the seed funding for *Insilico Medicine*, now a leader in the application of AI for Longevity research, drug discovery and development, and biomarker development. A MVP Panel of Biomarkers, hand in hand with highly integrated AI for data processing will make the biotech sector of Longevity much more lean, and dynamic. It will allow for a more rapid assessment period, which in turn will allow for a rapid succession of experiments with microdoses of different treatment and drugs, and then for translation into their parallel clinical applications, like preventive treatment in P4 Medicine or directly rejuvenation therapies in Regenerative Medicine.

It is important to develop and promote the widespread use of a comprehensive enough Panel of Biomarkers but, primarily, immediately actionable. We have documented many of the Aging Biomarkers here and identified from among them those which, by the metrics described, belong to the category we have named **Minimum Required:** the Most Viable Products for immediate implementation.

It is our hope that regardless of whether it is adopted wholesale, it may serve as a starting point for discussion on how best to utilize the deep knowledge we already have to maximum effect as soon as possible.



Sources Images: cbinsights.com | Rock Health

Report Methodology

Report Methodology in Details

To calculate the final score of a Single Biomarker or a Biomarker Panel, 3 types of Indexes are applied:

Accuracy Index - value expressed within the range [0.0-1.0].
It is a measure of the precision to predict overall biological age, based on the accuracy of each single biomarker scanned by the Panel. Thus, it is defined with formulas for both, single biomarkers and groups of biomarkers, and the output of the latter as an expression of the values projected by the first ones. The magnitudes depend not only on the number of biomarkers evaluated by the Panel, but on the nature of those biomarkers, the experimental background of its association with age-related conditions and processes, and a proposed classification framework that assigns or removes scores for qualitative characterizations; in this sense, the fundamental parameter used by the index is scientific support mined by sampling journal publications from specialized literature which successfully correlate each biomarker with temporary progression of aging. As expected, this framework equals the comprehensiveness of a biomarker or a panel with its precision or accuracy degree.

Availability Index - value expressed within the BAI range [0.0-10.0 BAI].
Value that is calculated by omitting the significance degree of the biomarker as an indicator of age-related health status, assuming the implicit condition of correlation between the biomarker and temporary progression of aging. It measures only the material capacity of extensive implementation for the reference character, understood as an expression of the availability of assays or tests, its invasiveness, monetary value, the proposed classification framework for qualitative characterizations used also in Accuracy Assessments, and so on.

Actionability Index - value expressed within the range [0.0-1.0].
Actionability is estimated as an expression of both the accuracy and availability of a biomarker or a Panel. The Availability Index value is transferred to the range [0.0-1.0]. Then, an operation is performed combining the previous measurements and converting them into a new metric that takes into account both factors; this is done by decreasing the absolute contribution of Accuracy Index, since it must be taken into account along with availability for assessment of actionability but does not contribute equivalently, being of lesser relative relevance in the terms described in the preceding pages. This comprehensive value allows to evaluate not only the current material capacity of implementation of a biomarker or a Panel but also its viability for biological age prediction in such an immediate and effective frame of implementation, thus empowering single biomarker and Panel comparisons with a purely pragmatic sense. It is a weighted expression of a biomarker or a Panel's individual and effective availability combined with a mathematical modification of its Accuracy Index that only admits near-real values for extremely high accuracy outputs of correlation with biological age, minimizing the contribution of said term for medium-high, medium and low magnitude outputs.

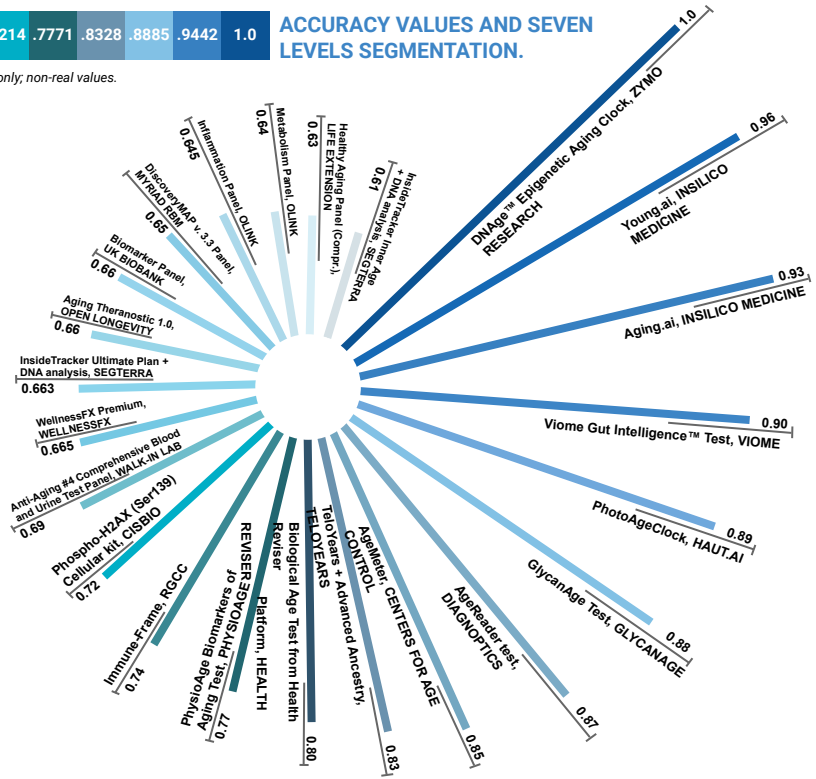
Indexes Values for Single Aging Biomarkers and Aging Panels

AGING ANALYTICS AGENCY

.6657 .7214 .7771 .8328 .8885 .9442 1.0

ACCURACY VALUES AND SEVEN LEVELS SEGMENTATION.

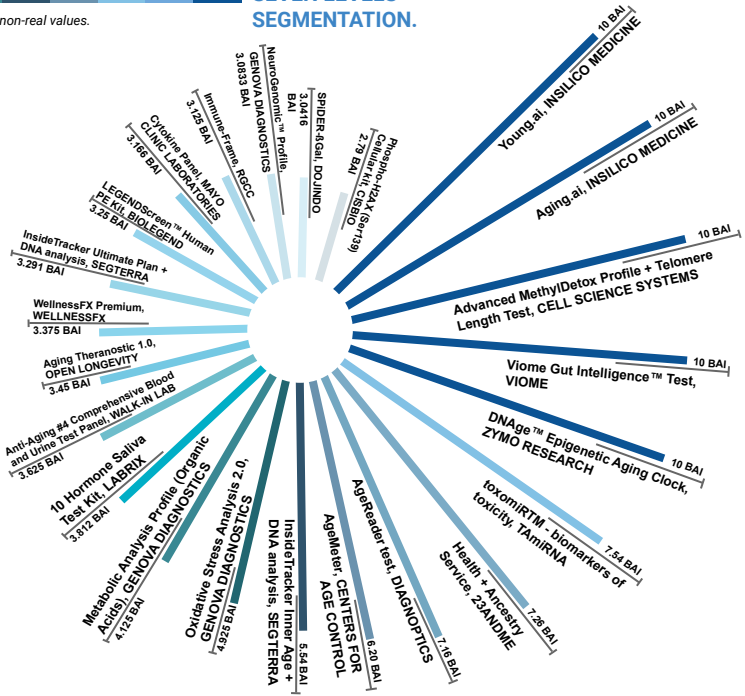
Illustrative only; non-real values.



3.82 4.85 5.88 6.91 7.94 8.97 10

AVAILABILITY VALUES AND SEVEN LEVELS SEGMENTATION.

Illustrative only; non-real values.

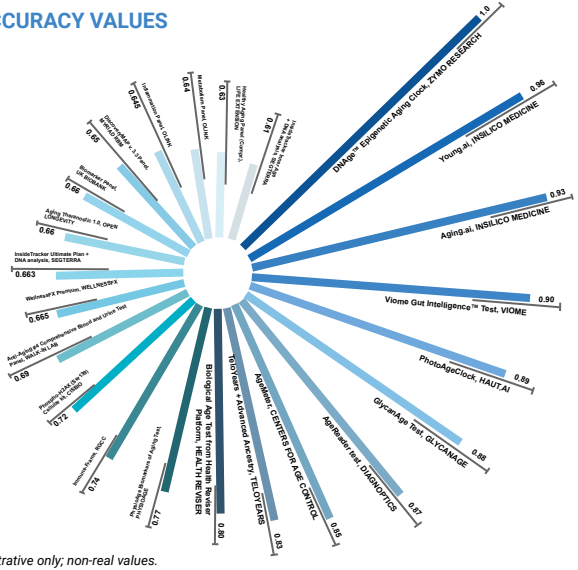


It is Aging Analytics Agency's hope that our comparative analytics framework and methodology will serve as a useful long-term analytical tool for aging single biomarkers and panels assessment to identify the most advanced, available and actionable resources to create, manage, optimize and improve action plans for the health and Longevity industry, market and public sectors.

Indexes Values for Single Aging Biomarkers and Aging Panels

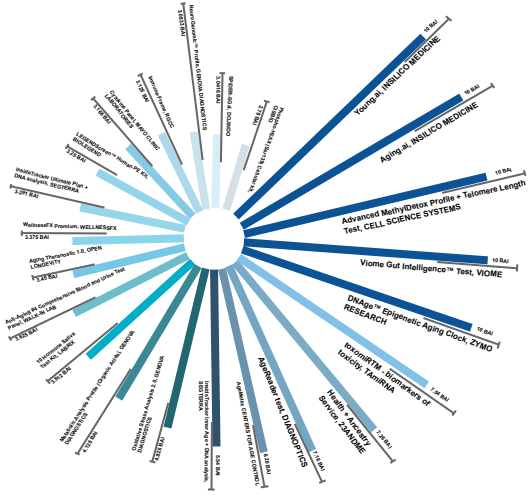
AGING ANALYTICS AGENCY

ACCURACY VALUES



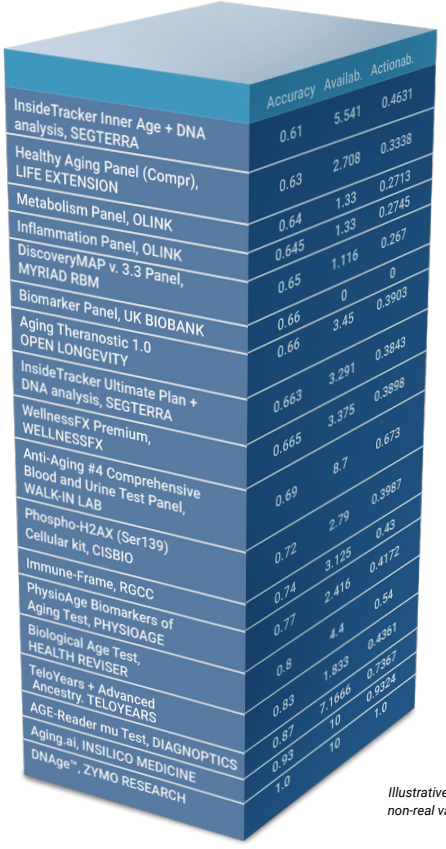
Illustrative only; non-real values.

AVAILABILITY VALUES



Illustrative only; non-real values.

ACTIONABILITY VALUES



Illustrative only; non-real values.

Aging Analytics Agency uses detailed mathematical procedures to assign a value (or numerical factor) to each of the three variables taken into account in the evaluation of single biomarkers and whole biomarker panels. Many qualitative considerations are made when assigning scores to these three variables. In first place, the **CONDITIONING STAGE CATEGORY** of the single biomarker or the panel; that is, if they are approved or not for clinical use. Second, its **OPERATIONAL CATEGORY**; if they are offered in the market as *laboratory research kits*, as *medical tests*; if the company gives *access to the prices*; if it is a *theoretical panel* or one *employed in epidemiological surveys*, in which case it is not materially offered to the market by the entity; if it is a *real-time evaluation technology for a set of biomarkers*, which could decrease availability due to the increase in cost but actually increases it because it allow large-scale assessment of vast amounts of patients, and so on. Thus, the numerical evaluation is to some extent subordinated to a multiplicity of qualitative factors considered by our highly specialized professionals in the field of biotechnology and pharmaceutical intelligence.

Indexes Values for Single Aging Biomarkers and Aging Panels

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NAME	COMPANY or ENTITY	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY	Accuracy Index (*)	Availability Index	Actionability Factor	Actionability Index (**)
Biomarker Panel	**UK BIOBANK**	Approved for Clinical Use	**Epidem. or Theoretical Panel Only** (BAI=0; ACTIONAB.=0)	0.66	0 BAI	N/A	**0**
DiscoveryMAP v. 3.3 Panel	**MYRIAD RBM**	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)	0.65	1.166 BAI	$(0.65)^2 + 0.1166 = 0.5391$	**0.2695**
Metabolism Panel	**OLINK**	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)	0.64	1.33 BAI	$(0.64)^2 + 0.133 = 0.5426$	**0.2713**
Inflammation Panel	**OLINK**	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)	0.645	1.33 BAI	$(0.645)^2 + 0.133 = 0.549$	**0.2745**
Healthy Aging Panel (Comprehensive)	**LIFE EXTENSION**	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)	0.63	2.708 BAI	$(0.63)^2 + 0.2708 = 0.6677$	**0.3338**
InsideTracker Ultimate Plan + DNA analysis	**SEGTERRA**	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)	0.663	3.291 BAI	$(0.663)^2 + 0.3291 = 0.7686$	**0.3843**
WellnessFX Premium	**WELLNESSFX**	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)	0.665	3.375 BAI	$(0.665)^2 + 0.3375 = 0.7797$	**0.3898**
Aging Theranostic 1.0	**OPEN LONGEVITY**	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)	0.66	3.45 BAI	$(0.66)^2 + 0.345 = 0.7806$	**0.3903**
Phospho-H2AX (Ser139) Cellular kit	**CISBIO**	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)	0.72	2.79 BAI	$(0.72)^2 + 0.279 = 0.7974$	**0.3987**
PhysioAge Biomarkers of Aging Test	**PHYSIOAGE**	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)	0.77	2.416 BAI	$(0.77)^2 + 0.2416 = 0.8345$	**0.4172**

Indexes Values for Single Aging Biomarkers and Aging Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY	Accuracy Index (*)	Availability Index	Actionability Factor	Actionability Index (**)
Immune-Frame	**RGCC**	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)	0.74	3.125 BAI	$(0.74)^2$ + 0.3125 = 0.8601	**0.43**
TeloYears + Advanced Ancestry	**TELOYEARS**	Healthcare-Ready	**Informational Purpose Test**	0.83	1.833 BAI	$(0.83)^2$ + 0.1833 = 0.8722	**0.4361**
InsideTracker Inner Age + DNA analysis	**SEGTERRA**	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)	0.61	5.541 BAI	$(0.61)^2$ + 0.5541 = 0.9262	**0.4631**
Health Reviser Platform	**HEALTH REVISER**	Approved for Clinical Use	**Biomarkers Real-Time Assessment Technology** (+5 Availability Weight Points)	0.8	4.4 BAI	$(0.8)^2$ + 0.44 = 1.08	**0.54**
Anti-Aging #4 Comprehensive Blood and Urine Test Panel	**WALK-IN LAB**	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)	0.69	8.7 BAI	$(0.69)^2$ + 0.87 = 1.3461	**0.673**
AgeReader test	**DIAGNOPTICS**	Approved for Clinical Use	**Biomarkers Real-Time Assessment Technology** (+5 Availability Weight Points)	0.87	7.1666 BAI	$(0.87)^2$ + 0.71666 = 1.4735	**0.7367**
Aging.AI	**INSILICO MEDICINE**	Healthcare-Ready	**AI Platform** (+5 Availability Weight Points)	0.93	10 BAI	$(0.93)^2$ + 1 = 1.8649	**0.9324**
DNAge™ Epigenetic Aging Clock	**ZYMO RESEARCH**	Healthcare-Ready	**Informational Purpose Test**	1.0	10 BAI	$(1.0)^2$ + 1 = 2	**1.0**

(a) Their respective values presented in this chart are illustrative only; they were not calculated based on their actual availability or accuracy. For real values, access the full Report.

Classification Framework for the Assignment or Removal of Scores by Qualitative Characterizations

AGING ANALYTICS AGENCY

(*) Accuracy results depend on the number of replicates for each biomarker per study and between studies, therefore it is expected that biomarkers with a lot of empirical support but few background studies (eg, gold standard ones; Horvath's Clock, Gut Microbiome Age Clocks, Advanced Glycation End-products Clocks) may have lower values than markers less correlated with aging but a large amount of experimental background (more replicas), like HbA1C, estrogens, testosterone and so on. The results, then, are always weighed against the total empirical support for each biomarker, which depends on the quality of the publications rather than merely the quantity, this being evaluated by our life sciences team at Aging Analytics Agency, highly trained in the analysis of Big Data from scientific publications.

(**) The numerical evaluation of Actionability is to some extent subordinated to a multiplicity of qualitative factors considered by our highly specialized professionals in the field of biotechnology and pharmaceutical intelligence. These qualitative considerations can be summarized in the following categorical delimitations:

- ***Research Use Only*** *Panels or Single Biomarkers: Availability Index is reduced in 2 Points, because it negatively conditions the implementation of the panel; there is little to no implementation of the Panel in healthcare assessment, even less in Longevity assessment.*
- ***Research Kits or Other Laboratory Practice Supplies (OLPS)*** *multiplies Accuracy Index by a RKOLPS coefficient (= 0.5) that causes the total value to fall, unless the supply is specifically designed for the evaluation of biological age or aging itself: these kits and OLPSs are not usually designed for this purpose, and evaluation of accuracy becomes highly subjective.*
- *A* ***Medical Test*** *Panel or Single Biomarker increases availability in 2 Points, but never exceeding the maximum 24 Points: facilitates large-scale implementation.*
- *A* ***Real-Time Assessment Technology*** *for a Biomarker or a Panel, increases availability in 5 Points, but never exceeding the maximum 24 Points: facilitates ultra large-scale implementation and analysis.*
- ***AI Platforms*** *for biomarkers inputs, increases availability in 5 Points, but never exceeding the maximum 24 Points: facilitates ultra large-scale implementation and analysis.*
- ***Epidemiological or Theoretical Panel Only*** *are those not in the market; they are references to scientific articles, or to academic developments or public developments not necessarily published in journals. The availability is 0 BAI, and in the same way actionability falls to zero (0); they are not part of the practical recommendations of this report.*
- *When* ***the company or entity does not share prices****, it is immediately assumed x> maximum tolerable in the calculation of Availability Index, thus causing the magnitude of the Availability Index to fall.*

Biomarkers of Longevity

Distribution by **Operational Category**

AGING ANALYTICS AGENCY

Research Kit or Other Laboratory Practice Supplies

- myriad RBM ImmunoMAP v.1.0
- myriad RBM AngiogenesisMAP v.1.0
- myriad RBM CytokineMAP A
- myriad RBM MetabolicMAP v.1.0
- myriad RBM DiscoveryMAP v.3.3 Panel
- myriad RBM CytokineMAP B
- myriad RBM NeuroMAP v.1.0
- myriad RBM InflammationMAP v.1.0
- myriad RBM CardiovascularMAP v.3.0
- myriad RBM Explorer MAP v.1.0
- myriad RBM HumanMAP v.2.0
- BioLegend LEGENDplex Human B Cell Panel
- BioLegend LEGENDplex Human Th Cytokine Panel
- BioLegend LEGENDplex Human CD8/NK Panel
- BioLegend LEGENDScreen Human PE Kit
- olink Cell Regulation Panel
- olink Cardiovascular II Panel
- olink Organ Damage Panel
- olink Cardiovascular III Panel
- olink Immune Response Panel
- olink Metabolism Panel
- olink Neurology Panel
- olink Neuro Exploratory Panel
- olink Cardiometabolic Panel
- olink Oncology II Panel
- olink Oncology III Panel
- olink Inflammation Panel
- ecosbio Phospho-H2AX (Ser139) cellular kit
- nanoString Human v3 miRNA Assay
- MIRXES MiRXES ID3EAL miRNA Assay
- abcam Senescence Detection Kit
- agilnoo SPiDER-ßGal

Medical Test

- Open Longevity Aging Theranostic 1.0
- WellnessFX WellnessFX Premium
- Walk-In-Lab Anti-Aging #4 Comprehensive Blood and Urine Test Panel
- InsideTracker Inner Age
- LifeExtension Healthy Aging Panel (Comprehensive)
- InsideTracker InsideTracker Ultimate Plan
- ZRT Female/Male Saliva Profile II - Test Kit for 6 Hormone Level Imbalances
- LabRFX 10 Hormone Saliva Test Kit
- FLUIDS iQ Adrenal Check
- GENOVA Oxidative Stress Analysis 2.0
- GENOVA NeuroGenomic™ Profile
- GENOVA Comprehensive Adrenal Stress Profile
- GENOVA Metabolic Analysis Profile (Organic Acids)
- GENOVA ImmunoGenomic® Profile
- GENOVA CardioGenomicPlus™ Profile
- Cell Science Systems Adrenal Stress Profile
- Cell Science Systems Advanced MethylDetox Profile + Thelomere Length
- Cell Science Systems Advanced MethylDetox Profile
- RGCC Immune-Frame
- RGCC aCGH RGCC
- PHYSIOAGE PhysioAge Biomarkers of Aging Test
- 23andMe Health + Ancestry Service
- MAYO CLINIC LABORATORIES Cytokine Panel
- ARUP Natural Killer Cell and Natural Killer T-Cell Panel
- ARUP CD57+ NK Cells, Peripheral Blood by Flow Cytometry
- ARUP CD21 (Dendritic Cell) by Immunohistochemistry
- ARUP B-Cell Memory and Naive Panel
- ARUP Cytokine Panel, TH1
- ARUP Regulatory T-Cell Panel
- ARUP Hepatic Function Panel
- ARUP CD4+ T-Cell Recent Thymic Emigrants
- ARUP Carnitine Panel
- ARUP Cytokine Panel

Informational Purpose Test or Platform

- Salimetrics Salivary Cytokine Panel
- ZYMO RESEARCH DNAge™ Epigenetic Aging Clock
- Osiris Green Epigenetic Age Analysis Version 2.0
- BioViva DNAge® Test
- HRG Targeted Seq. for DNA Methylation Analysis
- cerascreen Genetic Age Test
- HRG EpiLiver
- HRG EpiBreast
- CHRONOMICS EpiHealth
- HRG EpiAging
- HRG EpiSocialpsych
- GLYCANAGE GlycanAge Test
- VIOME Viome Gut Intelligence™ Test
- MICROBA Microba Insight™
- TFTAK Gut Microbiota Biohacker
- smartDNA smartGUT™ Microbiome Test
- LIFE LENGTH Telomere Length and Biological Age Testing
- TELOYEARS TeloYears + Advanced Ancestry Tests
- TAmiRNA toxomiRTM biomarkers of toxicity
- TAmiRNA thrombomiRTM biomarkers of platelet function
- Cell Science Systems Telomere Length Test
- TAmiRNA osteomiRTM validated bone biomarkers

Epidemiological or Theoretical Panel Only

- biobank UK Biomarker Panel
- Cytometry Part A Journal of Quantitative Cell Science ISAC — OMIP-004: In-Depth Characterization of Human T Regulatory Cells.
- Cytometry Part A Journal of Quantitative Cell Science ISAC — OMIP-007: Phenotypic Analysis of Human Natural Killer Cells.
- Cytometry Part A Journal of Quantitative Cell Science ISAC — OMIP-027: Functional Analysis of Human Natural Killer Cells.
- Cytometry Part A Journal of Quantitative Cell Science ISAC — OMIP-018: Chemokine Receptor Expression on Human T Helper Cells
- Cytometry Part A Journal of Quantitative Cell Science ISAC — OMIP-039: Detection and analysis of human adaptive NKG2C+ natural killer cells.
- Cytometry Part A Journal of Quantitative Cell Science ISAC — OMIP-029: Human NK-Cell Phenotypization.

Biomarkers Real-Time Assessment Technology

- Centers for Age Control AgeMeter
- Health Reviser Platform
- MEDIAGE MEDIAGE™ Biological Age Measurement System
- Diagnoptics AGE-Reader mu Test

AI Platform

- HAUT.AI PhotoAgeClock
- HAUT.AI Haut.AI Skin Health
- Aging.AI
- Young.AI
- CarePredict CarePredict Platform
- enlitic Enlitic Platform
- freenome Freenome Platform
- zebra AI-Powered Radiology Assistant
- PathAI PathAI Platform
- buoy Buoy Health Platform
- Tempus Platform
- BenevolentAI BenevolentAI Platform
- KenSci KenSci Platform
- zipongo Digital Nutrition Platform
- PROSCIA Proscia Platform
- ada Ada Symptom Checker app
- Google DeepMind Google's DeepMind Health AI Platform
- nourish balance thrive Blood Chemistry Calculator
- Better Better Therapeutics Platform
- babylon Babylon Health Platform
- iCarbonX iCabonX Platform

Biomarkers of Longevity

Distribution by **Conditioning Stage**

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Stage One: Research Use Only

- LEGENDplex Human Th Cytokine Panel
- LEGENDplex Human CD8/NK Panel
- LEGENDScreen Human PE Kit
- Freenome Platform
- ImmunoMAP v.1.0
- AngiogenesisMAP v.1.0
- CytokineMAP A
- MetabolicMAP v.1.0
- DiscoveryMAP v.3.3 Panel
- CytokineMAP B
- NeuroMAP v.1.0
- InflammationMAP v.1.0
- CardiovascularMAP v.3.0
- LEGENDplex Human B Cell Panel
- Salivary Cytokine Panel
- Explorer MAP v.1.0
- HumanMAP v.2.0
- Cell Regulation Panel
- Organ Damage Panel
- Cardiovascular II Panel
- Cardiovascular III Panel
- Tempus Platform
- Immune Response Panel
- Metabolism Panel
- Neurology Panel
- Oncology II Panel
- Oncology III Panel
- Neuro Exploratory Panel
- Cardiometabolic Panel
- Better Therapeutics Platform
- Inflammation Panel
- Phospho-H2AX (Ser139) cellular kit
- Human v3 miRNA Assay
- Senescence Detection Kit
- MiRXES ID3EAL miRNA Assay
- SPiDER-ßGal
- Proscia Platform
- BenevolentAI Platform
- OMIP-004
- OMIP-018
- OMIP-039
- OMIP-027
- OMIP-007
- OMIP-029
- ICarbonX Platform

Stage Two: Healthcare-Ready

- PhotoAgeClock
- Haut.AI Skin Health
- Aging.AI
- Young.AI
- Enlitic Platform
- Digital Nutrition Platform
- Salivary Cytokine Panel
- DNAge™ Epigenetic Aging Clock
- PathAI Platform
- Buoy Health Platform
- Epigenetic Age Analysis Version 2.0
- DNAge® Test
- KenSci Platform
- AI-Powered Radiology Assistant
- Targeted Seq. for DNA Methylation Analysis
- Genetic Age Test
- osteomiRTM validated bone biomarkers
- toxomiRTM biomarkers of toxicity
- EpiLiver
- EpiBreast
- EpiHealth
- Blood Chemistry Calculator
- EpiAging
- EpiSocialpsych
- GlycanAge Test
- TeloYears + Advanced Ancestry Tests
- Viome Gut Intelligence™ Test
- Microba Insight™
- Gut Microbiota Biohacker
- smartGUT™ Microbiome Test
- Telomere Length and Biological Age Testing
- thrombomiRTM biomarkers of platelet function
- Telomere Length Test

Stage Three: Approved for Clinical Use

- Aging Theranostic 1.0
- WellnessFX Premium
- InsideTracker Inner Age
- Anti-Aging #4 Comprehensive Blood and Urine Test Panel
- Healthy Aging Panel (Comprehensive)
- InsideTracker Ultimate Plan
- 10 Hormone Saliva Test Kit
- Adrenal Check
- Oxidative Stress Analysis 2.0
- NeuroGenomic™ Profile
- Female/Male Saliva Profile II - Test Kit for 6 Hormone Level Imbalances
- Comprehensive Adrenal Stress Profile
- Metabolic Analysis Profile (Organic Acids)
- ImmunoGenomic® Profile
- CardioGenomicPlus™ Profile
- Advanced MethylDetox Profile
- Adrenal Stress Profile
- Advanced MethylDetox Profile + Thelomere Length
- aCGH RGCC
- PhysioAge Biomarkers of Aging Test
- Health + Ancestry Service
- Immune-Frame
- Cytokine Panel
- Biomarker Panel
- CarePredict Platform
- Babylon Health Platform
- Health Reviser Platform
- MEDIAGE™ Biological Age Measurement System
- AGE-Reader mu Test
- Cytokine Panel, TH1
- Carnitine Panel
- Google's DeepMind Health AI Platform
- CD21 (Dendritic Cell) by Immunohistochemistry
- Regulatory T-Cell Panel
- CD57+ NK Cells, Peripheral Blood by Flow Cytometry
- B-Cell Memory and Naive Panel
- Natural Killer Cell and Natural Killer T-Cell Panel
- CD4+ T-Cell Recent Thymic Emigrants
- AgeMeter
- Cytokine Panel
- Hepatic Function Panel
- Ada Symptom Checker app

Biomarkers of Longevity

Distribution by **Amplitude Level**

AGING ANALYTICS AGENCY

Panels

InsideTracker Inner Age
InsideTracker Ultimate Plan
aCGH RGCC
RGCC Immune-Frame
Comprehensive Adrenal Stress Profile
B-Cell Memory and Naive Panel
Natural Killer Cell and Natural Killer T-Cell Panel
Health + Ancestry Service
Carnitine Panel
Cytokine Panel, TH1
Hepatic Function Panel
Regulatory T-Cell Panel
Cytokine Panel
Adrenal Check
Adrenal Stress Profile
Advanced MethylDetox Profile
Advanced MethylDetox Profile + Thelomere Length
AGE-Reader mu Test
Oxidative Stress Analysis 2.0
Cytokine Panel
Biomarker Panel
Aging Theranostic 1.0
10 Hormone Saliva Test Kit
Anti-Aging ±4 Comprehensive Blood and Urine Test Panel
Female/Male Saliva Profile II - Test Kit for 6 Hormone Level Imbalances
Healthy Aging Panel (Comprehensive)
CardioGenomic Plus Profile
ImmunoGenomic Profile
NeuroGenomic™ Profile
Metabolic Analysis Profile (Organic Acids)
PhysioAge Biomarkers of Aging Test
Metabolism Panel
Immune Response Panel
Cardiovascular II Panel
Cell Regulation Panel
Organ Damage Panel
Neurology Panel
Inflammation Panel
Cardiovascular III Panel
Neuro Exploratory Panel
Cardiometabolic Panel
Oncology III Panel
Oncology II Panel
HumanMAP v.2.0
MetabolicMAP v.1.0
CardiovascularMAP v.3.0
DiscoveryMAP v.3.3 Panel
AngiogenesisMAP v.1.0
NeuroMAP v.1.0
ImmunoMAP v.1.0
Explorer MAP v.1.0
InflammationMAP v.1.0
CytokineMAP B
CytokineMAP A
LEGENDplex Human CD8/NK Panel
LEGENDplex Human B Cell Panel
MiRXES ID3EAL miRNA Assay
Phospho-H2AX (Ser139) cellular kit
Senescence Detection Kit
SPIDER-βGal
OMIP-004
OMIP-018
OMIP-039
Salivary Cytokine Panel
LEGENDScreen Human PE Kit
LEGENDplex Human Th Cytokine Panel
OMIP-027
OMIP-007
OMIP-029
Human v3 miRNA Assay
smartGUT™ Microbiome Test
Genetic Age Test
Viome Gut Intelligence™ Test
Gut Microbiota Biohacker
toxomiRTM biomarkers of toxicity
Microba Insight™
GlycanAge Test
osteomiRTM validated bone biomarkers
thrombomiRTM biomarkers of platelet function

Single Biomarker

CD4+ T-Cell Recent Thymic Emigrants
CD57+ NK Cells, Peripheral Blood by Flow Cytometry
CD21 (Dendritic Cell) by Immunohistochemistry
EpiBreast
Telomere Length Test
DNAge™ Epigenetic Aging Clock
DNAge® Test
EpiHealth
EpiSocialpsych
EpiLiver
TeloYears + Advanced Ancestry Tests
Epigenetic Age Analysis Version 2.0
EpiAging
Targeted Seq. for DNA Methylation Analysis
Telomere Length and Biological Age Testing

Digital Panel Platform

Babylon Health Platform
Centers for Age Control AgeMeter
CarePredict Platform
Ada Symptom Checker app
Health Reviser Platform
Blood Chemistry Calculator
AI-Powered Radiology Assistant
Google's DeepMind Health AI Platform
MEDIAGE™ Biological Age Measurement System
KenSci Platform
Enlitic Platform
Aging.AI
Young.AI
PathAI Platform
Buoy Health Platform
PhotoAgeClock
Haut.AI Skin Health
Digital Nutrition Platform
Proscia Platform
Freenome Platform
BenevolentAI Platform
Better Therapeutics Platform
Tempus Platform
ICabonX Platform

Baseline Amplitude Level

Maximum Amplitude Level

Classification Framework by **Qualitative Characterizations**

It will be noted that our core Biomarker Domains Classification Framework is absent in the previously exposed Classification Framework by Qualitative Characterizations; although the first systematization is applied throughout the entire report, particularly in the profiles of Single Biomarkers and Panels, it does not affect the scores of Single Biomarkers and Biomarker Panels at the time of its quantitative evaluation. The Biomarker Domains Classification Framework is related only to characteristics of the selection process of the Panels offered by the market. Those Panels conform to the Three Spectra Classification Framework exposed in the previous boxes; nevertheless, these three spectra precise and advanced systematization is not enough, as detailed below.

The vast majority of the Panels offered by the market evaluate characteristics at a molecular level and based on laboratory procedures. For instance, there are almost no commercial presentations for assessment of Cognitive Function; there are isolated neurological or psychological tests not addressed by Biomarker Panels in the market. The same applies with Physical or Physiological Function assessments; classic imaging tests, ultrasound, waist circumference, muscle mass, bone density, grip strength and so on, are almost not included variables in the Panels offered by the market; in this sense, the only Panel for assessment of those conventional variables is a traditional Physical Examination -or Comprehensive Physical Exams sensu stricto-; that is, checkups provided by clinical physicians, neurologists, and so on. In those cases, our Panels selection would overlap entirely with the offer of clinical and specialized medical services related to these specific domains; it should be considered that a physician's service is a Panel per se, or something similar to that. And which of those "Panels" for Physical, Physiological or Cognitive function would we choose? There are as many as physicians. It will also be noted that most of the Biomarker Panels cannot be characterized with a Domains Classification Framework, since the majority include Biomarkers distributed between these three Domains - some of Endocrine Function in conjunction with others of Immune Function and sometimes with some of our Molecular Level Domain-.

Nor can we omit these Biomarker Domains. In Aging Analytics Agency we propose an exhaustive and advanced evaluation of all the variables that influence the aging process and Longevity, and for that reason we have included this Biomarker Domains Classification Framework. For this considerations, it has been decided to recommend a combination of all these categories; the following configuration for the most optimal Panel, the one with the best availability vs. accuracy ratio: one that includes data from conventional physical, physiological and cognitive exams, offered by the clinical services - and for which only an accuracy assessment is carried out, since its availability is, with certainty, maximum; or at least in the countries with access to the minimum expected clinical services-, and additionally data provided by Panels that evaluate Immune, Endocrine and other Molecular and Cellular Level Biomarkers, the remaining three domains that are satisfied by the offer of Biomarker Panels in the market.

Distribution by **Conditioning Stage**

- The Conditioning Stage Classification Framework allows to differentiate degrees of availability vs. accuracy in strata or layers according to the current state of Panels uses.
- **Research Use Only** Panels and tests, as immunophenotyping of T cells, B cells and so on, could be highly decisive for aging and Longevity assessments, nevertheless there is virtually no availability for healthcare evaluations. Sometimes they are used, but only in very particular health conditions and frequently at the cost of making mistakes: the methodology is usually not well standardized, the results are sometimes confusing, the association with aging conditions and Longevity is not so linear or clear. At the same time, RUO Panels are often very expensive ones; ELISA kits, chromatographic assays or those involving NMR, and other laboratory kits not usually used in clinical practice. Here, poor availability and poor accuracy overlap; this is the stratum that worse availability vs. accuracy ratio per Biomarker would have. Aging Analytics Agency does not intend to exclude these presentations from the practical purposes of its studies; here we consider Panels such as those offered by Olink, BIOLEGEND, Myriad, all companies and products deeply involved in P4 Medicine as they facilitate the study and assessment of the proteome specifically, and other-omic levels in general.
- Routine and **Approved for Clinical Use** tests for our selected Single Biomarkers have usually a high correlation degree with age-related diseases and aging conditions; they often show good availability and excellent actionability. We could focus mainly on these, but what will provide an increase in their precision and utility for Longevity assessments is to combine them with the so-called "Healthcare-Ready" Panels.
- **Healthcare-Ready** tests (or "Used for Informational Purposes" tests) are those RUO sensu lato; although they are not Approved for Clinical Use - as they lack clinical validity at some degree-, they are offered by companies and clinics to give complementary information on the state of health or Longevity. Thus, they may or may not provide useful information, which should be analyzed in conjunction with data provided by validated, ACU tests. This category has good general availability, despite constituting Non-Approved for Clinical Use presentations; so they are considered quantitatively equivalent to ACU in availability calculations, but without being ACU at a qualitative level. Healthcare-Ready Panels are almost ready for the healthcare market, although they are not implemented in these terms: they have an informative purpose only. Nevertheless, its continuous use in such configuration and in conjunction with already validated Panels will allow a better interpretation of the outputs or endpoints, enhanced standardization of the results, wide access to the products, and therefore its very prompt clinical validation. The increasing access of individuals to this presentation stratum is an incredible new phenomenon in regard to the health care market; it should be used to introduce health endpoints in Digital Panel Platforms already conditioning for assessments of biological age, aging itself and Longevity; that is, in a way that other RUO Panels are not yet ready to achieve.

Distribution by **Amplitude Level**

- An analytical and comparative approach of aging biomarkers makes it necessary for certain single ones to be considered as equivalent to whole Panels, since they are strongly and self-sufficiently correlated with chronological age. This is the case regarding some classic examples such as telomere length assays (*Telomere Length Test* from Cell Science Systems; *Telomere Length and Biological Age Testing* from Life Length) or CpGs dinucleotides Methylation tests (*DNAge™ Epigenetic Aging Clock* from Zymo Research; *Epigenetic Age Analysis Version 2.0* from Osiris Green), among others. The single biomarkers selected in this report are almost always significantly correlated with chronological age - they are indicators of biological age on their own-, although not usually with particular pathologies and conditions associated with the progression of aging; thus, its clinical interpretation or validity is usually limited. The dramatic reduction in costs for most of these advanced assessments allows those biomarkers to be currently used for informational purposes complementary to clinical validity tests, having good availability. In the other hand, a few single biomarkers selected as Panels do not present such correlation with chronological age; they would only describe it to some extent, or not, depending on their calculated accuracy index.

- In the same way, in a market study it can be seen that some of these Single Biomarkers are not integrated in Panels which also justifies this criterion. These forms of presentation are at an equivalent amplitude level regarding to their correlation with chronological age; in practice, one of these Single Biomarkers can be equivalent, in terms of Accuracy for biological age assessment, to an entire Panel.

- A **Digital Panel** is a platform in which data sets from Digital Biomarkers and non-Digital Biomarkers (eg, blood, physical, physiological or other tests outputs) are introduced and integrated by an algorithm and analyzed to establish a biological age secondary output, allowing a real-time health status assessment. Note that they include Digital Biomarkers, but are not restricted to them; they also include AI platforms, but not limited to these.

- **Real-time monitoring combining Single Biomarkers and entire Panels from different sources provides a much higher level of amplitude** (or **comprehensiveness**) than the other two presentations; for this case study, highly consolidated Platforms only have been considered, this is, in terms of their documented precision and reliability. Thus, all of them have comparatively a maximum degree of amplitude, or maximum Accuracy (1.0), with availability being the conditioning factor of actionability.

Open Access and Proprietary Metrics

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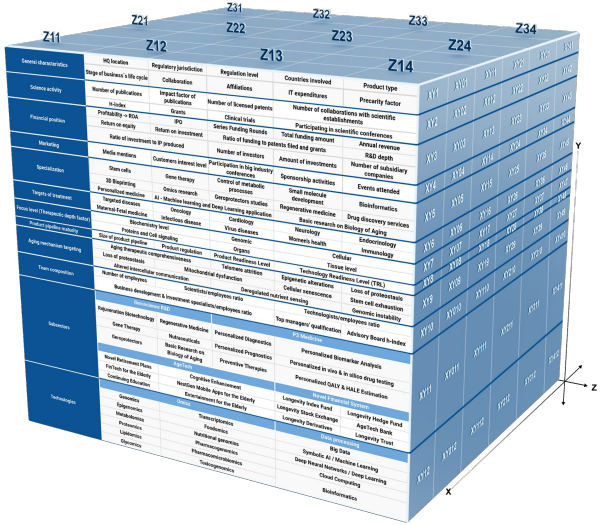
Open Access Metrics



Proprietary Metrics

The methodology and metrics featured in this teaser for this contracted analytical case study are public and could have been used in a number of other open-access Aging Analytics Agency reports, whereas a large portion of the analytical frameworks used for the report's benchmarking are proprietary, available to potential partners via NDA. These include both absolute values (quantitative or qualitative) and dynamic parameters to analyze metrics as they change over time. The following are examples of parameters used in assessment of P4 Medicine clinics, so many of them may concern this report while others may not.

The Role of AI in Biomarker Discovery and Monitoring

The Increasingly Necessary Role of AI in Longevity Research

- As with the Rejuvenation Biotechnology 10 years ago, today the technology again is ahead of the policy, and the practical healthcare and medical frameworks of developed countries, necessitating a paradigm shift toward greater prevention, personalization, precision and patient participation, utilizing all available tools and technologies that are market-ready today to optimize citizens' Healthy Longevity.
- The layering of paradigms, and the explosion of synergies that Data Aggregation in healthcare will produce within a short timeframe, means that by the normal methods of assessment, the science of Longevity will soon be comprised of tens of thousands of components, and to predict the effects of all of them on human health is already an incredibly complex challenge. The major tool for managing this will be AI. Hence why Aging Analytics Agency have long considered AI the major engine and driver of future Longevity science and industry.
- This is especially true of P4 medicine itself. P4 is defined by the fact that its constituent leading-edge technologies have already achieved a state of market-readiness and clinical implementation. As such, when different strands of geroscience R&D reach a state of validation sufficient for their practical implementation, they cross over from R&D and into the scope of P4 medicine.
- Given that P4 medicine, by definition, consists of those Longevity-relevant technologies and techniques that are in practice today, what remains to be done in terms of actually applying them for the extension of Healthy Longevity is largely a matter of data mining, analysis and management, driven by advances in biomedicine, data science and Artificial Intelligence.
- For example, as AI for R&D in drug discovery becomes more sophisticated, drugs will become more customized to specific diseases and even specific patients. Drug development companies will transition from the current form of "blockbuster drugs" (standard drug formulations applicable to many millions of patients) to P4 medicine, tailoring drugs to specific patient cases based on age, gender, ethnicity, state of health and genetics.

Deep Aging Clocks: deep-learned predictors of Biological Age

- Holistic view into biological processes
- Dementia screening and staging
- Feature transfer from aging to disease
- Regenerative medicine
  - Patient age-matching
  - Stem-cell quality control
- Generation of synthetic data
- New targets identification
- P4 Medicine to P6: Intelligent Health Web Science
- Reproductive longevity tracking
- Age-adjusted clinical trial enrolment
- Age-personalized immuno-oncology monitoring
- Age-personalized vaccines
- Health trajectory monitoring and estimations
- Mortality prediction
- Immunosenescence analysis
- Digital clinical trial outcomes predictions
- Age reversal

The Increasingly Necessary Role of AI in Longevity Research

The first and second *Ps* in P4 Medicine are **personalized** and **precision**, which refer to the drugs and treatments that will be designed and applied using precise, individually-tailored methods of dosing, cocktail compositions of micro-dosages, and efficient methods of delivery. Such advances also represent a move toward greater **prevention** (the third *P* in P4 Medicine), and a shift away from reactionary treatments and towards optimized disease prevention, by the application of micro-dosages of drugs long before the underlying pathology develops into actual chronic disease. Healthy Longevity means prevention rather than treatment, through the maintenance of optimal states of health via continuous monitoring of Biomarkers, and micro-adjustments in therapeutic, lifestyle and behavioural regimes to normalize those Biomarkers.

The fourth *P* in P4 Medicine is **participatory**, which refers to the increasingly active role that patients are taking in managing their own health, culminating in a situation where citizens are empowered with the tools, approaches and services capable of enabling continual micro-adjustments to their behavioural, lifestyle and therapeutic regimens in response to continuous AI-empowered monitoring of micro-changes in Biomarkers that measure state of health and predict risk of diseases long before their actual onset and progression.

These changes are already being embraced by the medical communities and healthcare systems of progressive countries. In coming years, as P4 becomes the new norm, the new definition of failure will be when patients are forced to get doctors involved. In a world in which P4 Medicine triumphs, citizens will have no need to engage with doctors until the very end of life. The term “Precision Health” is becoming increasingly common. The term refers to the idea that the ideal and most comprehensive case of P4 Medicine will naturally and inevitably lead to a state of Precision Health, where diseases and other sub-optimal forms of health are delayed for as long as possible, until near the very end of life.

The role of AI in P4 Medicine is already remarkably apparent, especially in places such as the UK, USA, Switzerland and Singapore. For example we have seen very proactive efforts by the UK government, both through their AI Industrial Grand Challenge and their Aging Industrial Grand Challenge, to rapidly apply AI to preventive medicine, advanced biomedicine and Digital Health, and the recent establishment of the All-Party Parliamentary Group for Longevity, where Aging Analytics Agency was proactively involved.

Biomarkers and Data Science in the Core of P4 Medicine

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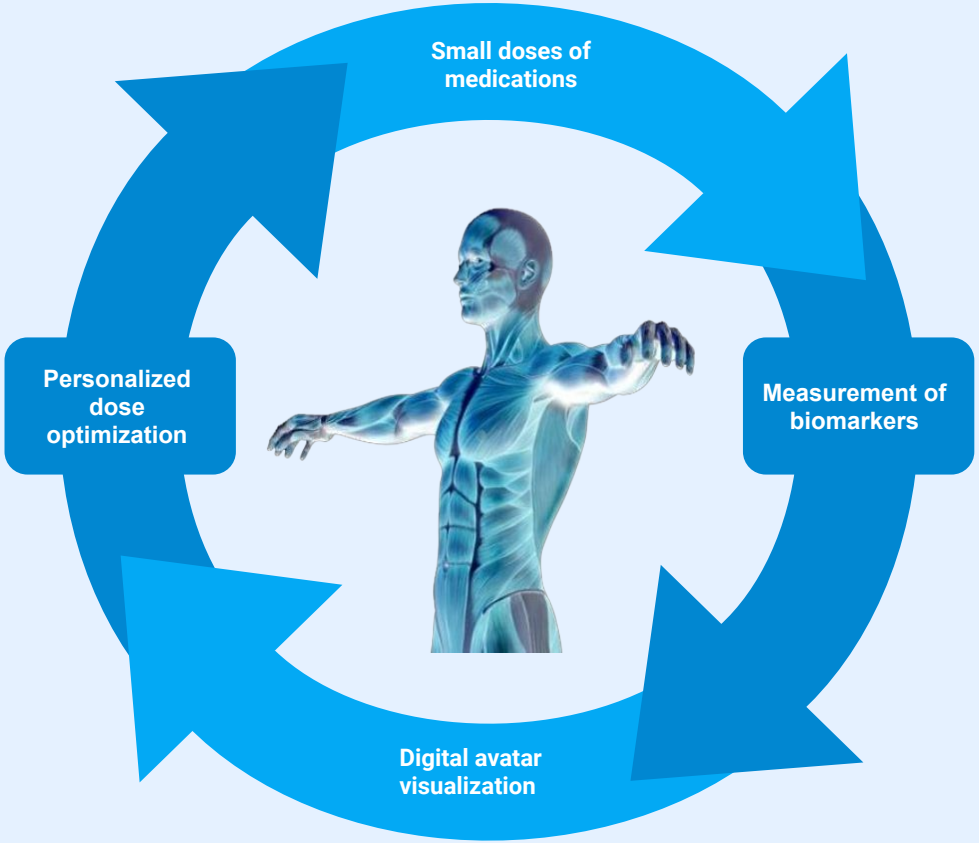

Not only do new methods of standard industry benchmarking and forecasting need to be developed to combat the issues of overcomplexity and multidimensionality in the Longevity Industry, but new methods of testing the basic safety and efficacy of Longevity and Precision Health prevention, diagnostics, 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.

Precision Diagnostics

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Digital avatar visualizes a combination of Biomarkers and other diagnostic results

Collect your data today:

- Blood samples
- Biomarker analysis
- Database of personal biomedical data stored on blockchain

Future benefits:

- Data driven analysis of Biomarkers dynamics over time
- Analyse the changes in your digital avatar
- Personalized interventions

A large part of health information is digitized, which allows us to compile enormous amount of data, access global servers, and compare patient information, sort of a dynamic repository of information that is constantly being updated. The massive advance as far as these databases facilitates doctors in their diagnostic process, their ability to measure, analyze, compare patients, and produce medical reports that are more accurate and personalized, that will, in turn, lead to the best available therapy or treatment of the time.

The intensive application of AI to all stages of Longevity and Preventive Medicine R&D, and healthcare, has the potential to rapidly accelerate the clinical translation of experimental, validated and non-validated biomarkers, toward diagnostics, prognostics and therapeutics, to empower patients to ultimately become the CEOs of their own health through continuous AI-driven monitoring of minor fluctuations in biomarkers, and the rapid development of the global Longevity Industry to scale.

Sources: Digital Health. Fundación Innovación Bankinter.

Data Science for Biomarkers

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- Multi-Omics Sequencing
- Multi-modal total body Imaging
- Qualitative functional tests
- Data from wearable devices

The diagnostic technologies of the future are grounded in colossal bodies of data which are incomprehensible by current linear methods, and that will span every stage in the development of a pathology, from the exposome to the epigenome.

- Non-invasive continuous monitoring of biomarkers
- 3D integration of cross-sectional tissue and organ imaging
- Whole-body and organ specific biological age calculation based on biomarkers

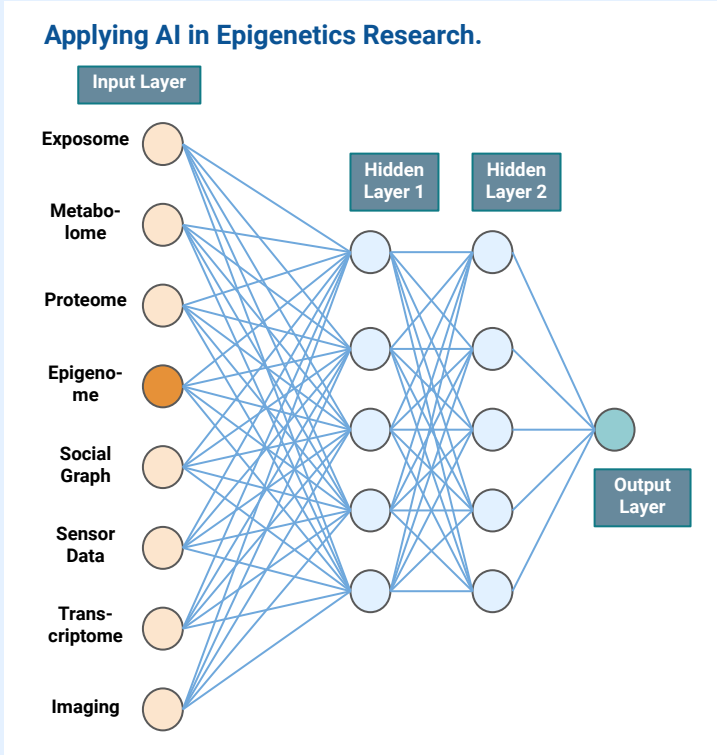
To shorten that translation delay from Research Use Only (RUO) and non-validated biomarkers and panels, to an Approved for Clinical Use (ACU) condition in the field of age-related diseases health care, and for a deep impact on applied health in a world of aging populations, it is an essential challenge, to obtain a set of biomarkers already Approved for Clinical Use with high availability and actionability, and use it in conjunction with others, market- and healthcare-ready although less conventional biomarkers gathered in digital real-time monitoring environments. **That will enable a sufficiently accurate assessment of the overall process of aging, calculation of biological age, and analysis of the progression of particular elderly conditions nested by biomarker networks leading to the creation of a Most Viable Product, or the Minimum Required Panel.**

Biomarker networks, which consist of the alignment between interactome and phenome levels, reveals new disease genes and connections between previously unrelated diseases or traits. Despite a great potential for novel discoveries, this approach is still rarely used in genomics and other *omics*. A biomarker network is a group of functionally related units of indicators, of any biological level, that contribute to the same phenotype - understanding by *phenotype* a molecular, metabolic, immune, physiological or physical trait, and so on-, pathological or not. The *interactome* - the whole set of molecular interactions for a trait, a condition, a disease, a cell or another biological unit-, and the *phenome* - the set of all phenotypes expressed by that unit-, are complexly connected at multiple levels. At the root of these networks is the epigenome. Only AI-driven methods can efficiently address such complexity, those colossal bodies of data that can be currently entered into multiple and different digital platforms.

Data science and AI making Complex Biomarkers available

AGING ANALYTICS AGENCY

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. We are in the initial stages of a revolution in precision medicine enabled by advanced technologies such as epigenomics, AI, and blockchain. The pioneering effort by early adopters from the research space is critical for putting these technologies within reach of the broader healthcare ecosystem.



Multilevel artificial neural network to support epigenetics research. 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.

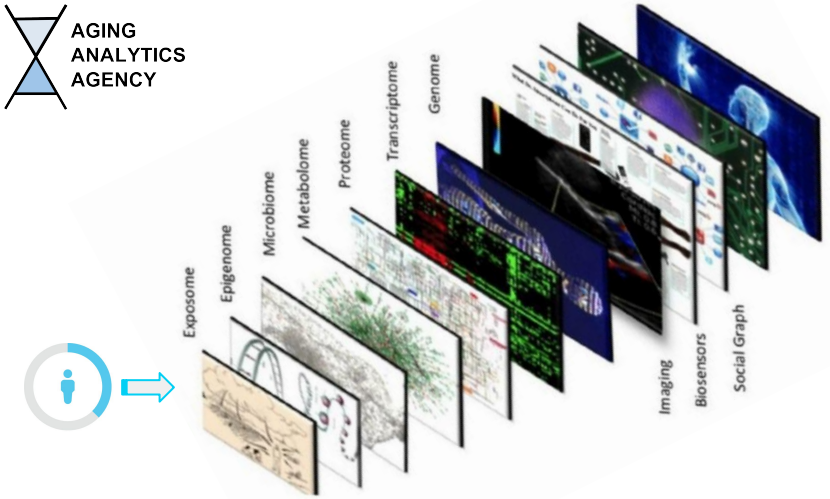
Sources: Schumacher, A. Epigenetics of Aging and Longevity. *2018.*

Data science and AI making Complex Biomarkers available

Systems healthcare is a holistic approach to health premised on systems biology and medicine. The approach integrates data from molecules, cells, organs, the individual, families, communities, and the natural and man-made environment. Both extrinsic and intrinsic influences constantly challenge the biological networks associated with wellness. Such influences may dysregulate networks and allow pathobiology to evolve, resulting in early clinical presentation that requires astute assessment and timely intervention for successful mitigation.

The cornerstone of P4 Medicine, as in systems health, is the evaluation of dysfunctions of molecular or biomarker networks. The P4 Medicine paradigm involves a comprehensive understanding of the regulation and dysregulation of the complex molecular networks that forge the phenotype of an individual. In this framework, disease is a consequence of aberrant reconstitution of cellular and molecular networks that lead to organ and organismal dysfunction (e.g., the patient's clinical presentation).

AGING ANALYTICS AGENCY



Creation of topological maps of health and disease.
"Omic" latin suffix, or "ome" = mass or many.

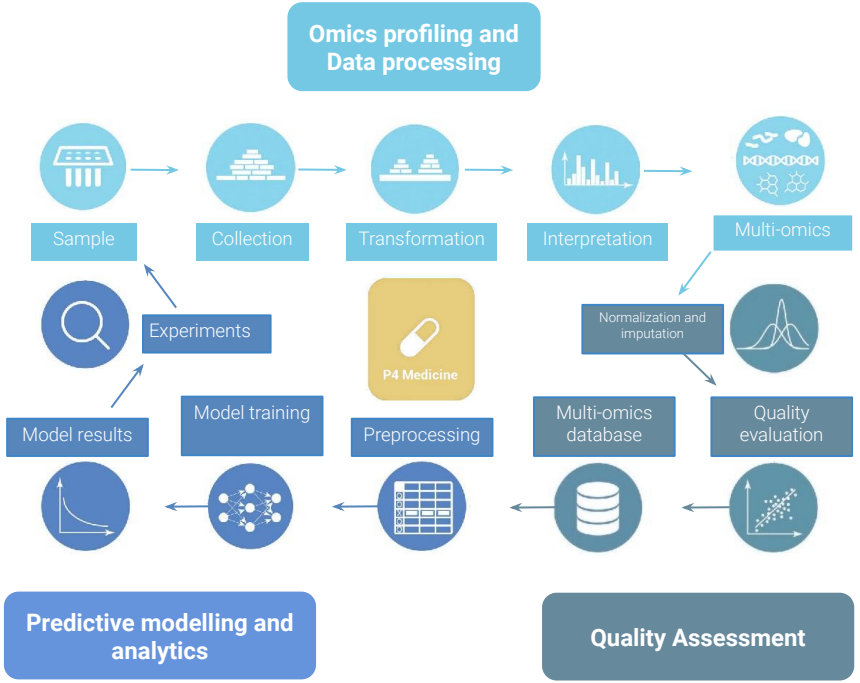
The interaction of the diseased organ within the person produces a cascade of dysregulated networks, resulting in associated comorbidities, some of which are evident and others that are asymptomatic (preclinical). In the state of wellness, networks are precisely regulated via complex homeostatic mechanisms. Through one or a series of network (or sub-network) perturbations, wellness is driven toward altered nodal activity. Such nodal modulation constitutes the at-risk state, and although preclinical, it typically provides systemic signatures, which can be discerned and quantitated, and enable detection of dysregulation during a preclinical stage. Systems level wellness, disease prevention, and health, therefore, aim to characterize specific nodal perturbations, some environmentally mediated, others rooted in the complexities of the intrinsic multidimensional networks only revealed via the aforementioned perturbations.

Sources: Fiandaca M. S., et al. Systems healthcare: a holistic paradigm for tomorrow. *2017.*

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 compendia 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.

Sources: Minseung Kim, et al. Data integration and predictive modeling methods for multi-omics datasets. *2017.*

Data science and AI making Complex Biomarkers available

Machine and Deep Learning analytics over integrated multi-omics data have the capacity to make far-reaching impacts across multiple industries. In biomedical applications, finding therapeutic targets and biomarkers is one of the major issues in human health, and such efforts are being more and more translated into the real world (e.g. BERG, Eagle Genomics). Antibiotic resistance is of paramount importance as it is considered a global threat and machine learning methods can be applied for predicting antibiotic resistance from the molecular signature of clinical isolates to select effective antibiotics. In food and nutrition science, optimizing nutrition treatment for individuals is enabled by machine learning over personal omics data accompanied with dietary information.

One prominent example of applying deep learning comes from gaming. In 2016, the program AlphaGo beat the world champion Lee Sedol in four out of five games of Go, a complex ancient Chinese board game. It was a huge victory for AI that came decades earlier than most experts believed possible. AlphaGo was developed by DeepMind, a subsidiary of Google that focuses on AI. Instead of relying on explicit programming, DeepMind applies general-purpose learning algorithms to large data set to make predictions. It is this type of advancement in machine learning that is delivering on the promise of real-time diagnostics and revolutionizing the future of precision medicine. In the same year, the field of machine learning changed significantly because most of the major information and communication technology (ICT) companies have made their deep learning codes open source and available to anyone. Consequently, most major machine learning implementations are available for free to use and modify for everybody. This means it is possible for all researchers to set up a simple machine intelligence with nothing more than a laptop and a web connection. Already, there are over 50 different deep learning tool sets available and most are already open source.

As a key case study that cannot be omitted, some early approaches to merge epigenetics and deep learning exist already. One of them is DeepCpG, which was designed to help scientists learn about the connections between genomic data and DNA methylation to make predictions about DNA methylation in single cells. In particular, DeepCpG is trained to predict binary CpG methylation states from local DNA sequence windows and observed neighboring methylation states. The trained DeepCpG model can be used for different downstream analyses, including imputation low-coverage methylation profiles for sets of cells and discovery of DNA sequence motifs that are associated with methylation states and cell-to-cell variability. The long-term goal of using deep learning algorithms is to predict the effect of epigenetic drift and epimutations on a cell's regulatory landscape and how this, in turn, affects disease development. And aging itself.

Sources: Minseung Kim, et al. *2017.* | Schumacher, A. *2018.*

AI-Driven Biomarkers and P4 Medicine

AGING ANALYTICS AGENCY

AI-Driven Precision Biomarkers

- Multi-Omic Sequencing
- Continuous monitoring powered by Big Data Analytics
- Continuous monitoring of health state based on changes in Biomarkers of aging

AI-Driven Advanced Prognostics

- AI-driven prognostics
- Advanced Biomarker-based prognostics
- AI-driven predictive prognostics based on personalized multi-omics

Personalised Treatment Optimization

- AI-driven *in silico* personalised treatment optimization
- AI-driven personalised in vivo drug optimization
- Treatment optimization based on patient genetics

AI-Driven Preventative Treatment

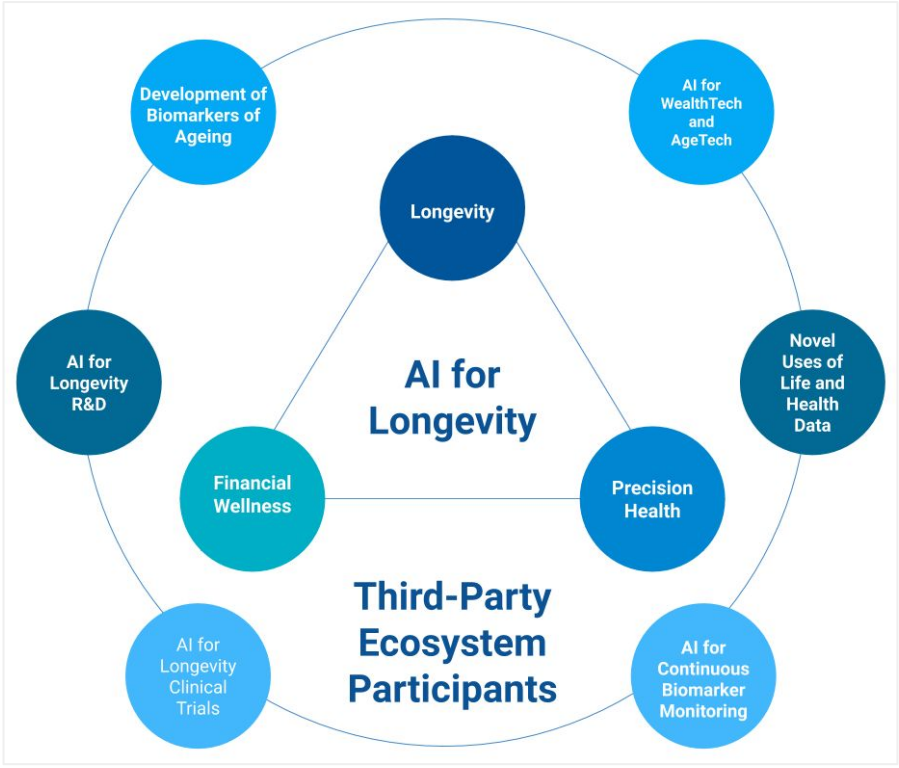
- Maintenance state of precision health through preventive medicine
- AI-based predictions of optimal drug combination

Data science and AI making Complex Biomarkers available

Key points:

- As the complexities of Longevity science and technology increase, and as the volume of data continues to amass, the role of AI in both analyzing and understanding becomes completely necessary for continued progress and industry development
- While AI for Longevity is still an emerging and underrepresented sector within the global Longevity Industry, its extreme disruptive potential makes its eventual emergence as a core and integral area of growth and development inevitable
- 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 apparent in almost every sector, from Longevity R&D to therapeutic development, P4 Medicine, biomarker discovery, and even non-biomedical sectors such as the Longevity Financial Industry.

Awareness of the importance of utilising Artificial intelligence within aging and longevity research is rapidly increasing in academia and industry. Modern deep learning techniques used to develop age predictors offer new possibilities for diverse data types. This will enable a holistic view to identify novel biomarkers, but it will also bring novel geroprotectors and will become the core of drug discovery and healthcare in biotechnological, pharmaceutical and health industries, integrating them like never before.

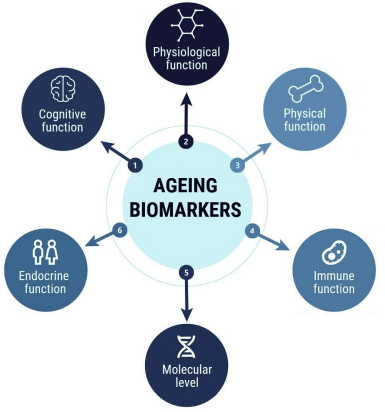


Selected Biomarkers by Comprehensiveness Level

Selected Biomarkers List

AGING ANALYTICS AGENCY

1. Gait (Walking) Speed
2. Timed Get Up and Go
3. Chair Rising
4. Grip Strength
5. Standing Balance
6. Purdue Pegboard Test
7. Spirometry: Forced Expiratory Volume in 1 Second (FEV1)
8. Bone Density, Bone Mass Hip: Dual X Ray Absorptiometry for Bone Health
9. Broadband Ultrasound Attenuation (BUA) at Heel for Bone Health
10. Computed Tomography for Bone Health
11. Dual X Ray Absorptiometry for Estimated Leg Muscle Mass
12. Bioelectrical Impedance Analysis for Muscle Mass
13. Computed Tomography for Muscle Mass
14. Magnetic Resonance Imaging for Muscle Mass
15. Body Potassium for Muscle Mass
16. Abdominal Fat; Waist Circumference
17. Body Mass; Body Mass Index; Body Weight
18. Blood Pressure; Sphygmomanometry
19. Standard Lipid Profile: Total Cholesterol; LDL-C; HDL-C; Triglycerides
20. Glycated haemoglobin (HbA1C)
21. Fasting Plasma Glucose
22. Verbal Fluency
23. Digit-Symbol Coding
24. Digit Span Backward
25. Boston Naming Test
26. Stroop Task
27. Block Design Test
28. Raven's Progressive Matrices
29. Rey Auditory Verbal Learning Test
30. Benton Visual Retention Test
31. Adiponectin
32. DHEAS:Cortisol Ratio
33. DHEAS
34. Growth Hormone; IGF-1
35. Leptin
36. Ghrelin
37. Melatonin
38. Estrogens
39. Somatostatin
40. Testosterone
41. Thyroid Hormones
42. B Cells
43. CMV Seropositive
44. C-Reactive Protein
45. Dendritic Cells
46. Natural Killer Cells
47. Neutrophils
48. Lymphocyte/Granulocyte ratio
49. Immune Risk Profile
50. Telomere Length in Leukocytes
51. T Cell Phenotype
52. CpGs Dinucleotides
53. miR-34a
54. miR-1, miR-133a, miR-499 and miR-208a
55. miR-137, miR-181c, miR-9, and miR-29a/b
56. IFN-γ
57. High-Sensitivity C-Reactive Protein (hs-CRP)
58. Lipoxins
59. TNF-α
60. IL-1
61. IL-6
62. IL-10
63. IL-12
64. p16INK4a
65. β-galactosidase
66. Small Dense Low-Density Lipoprotein (sdLDL)
67. High Density Lipoprotein (HDL)
68. AGEs
69. NT-proBNP
70. γ-H2A.X
71. Protein Carbamylation
72. Mitochondrial DNA Copy Number
73. Cell-Free DNA
74. Telomere Length Aging Clock
75. Biomarkers of Oxidative Stress
76. Gut Microbiome Transcriptome

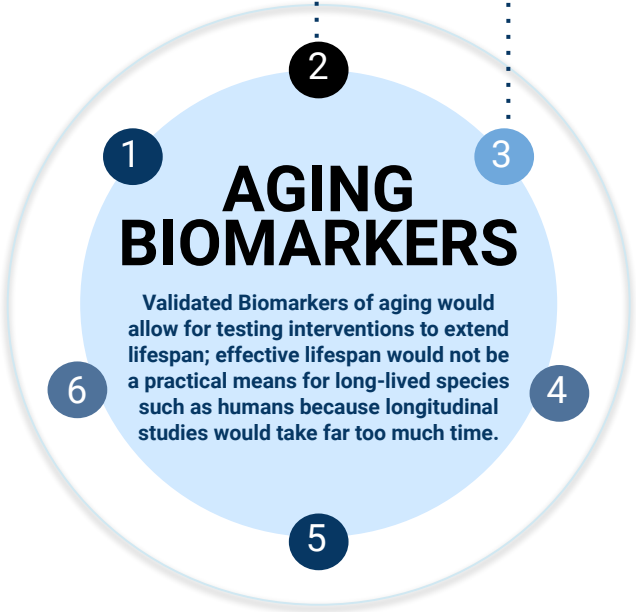


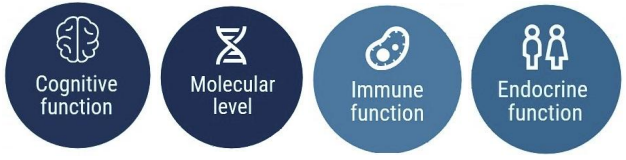
Biomarker Domains Classification Framework.
Biomarkers of Physical Function and Physiology.

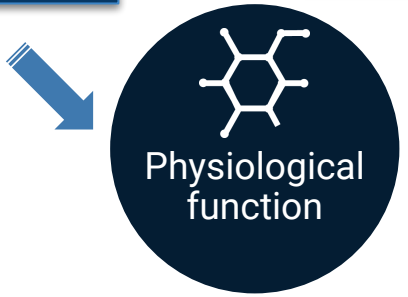
AGING ANALYTICS AGENCY

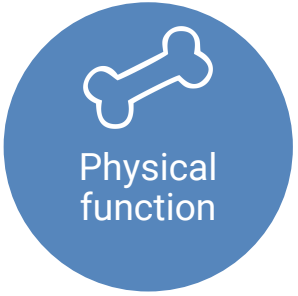
Biomarkers of Physical Function and Physiology

Complex changes affecting the structure and function of cells, tissues and organ systems are a hallmark of aging and can be detected by the third or fourth decade of life. These may translate, eventually, into functional loss, chronic disease and finally death.









Body Composition.
Muscle mass: Bioelectrical Impedance Analysis; Computed Tomography; Dual-energy X-ray Absorptiometry; Magnetic Resonance Imaging; Body Potassium.
BMI.
Body Weight.
Waist Circumference and abdominal fat.

Bone Health.
Broadband Ultrasound Attenuation.
Computed Tomography.
Dual-energy X-ray Absorptiometry.
All have been used extensively to measure bone health.

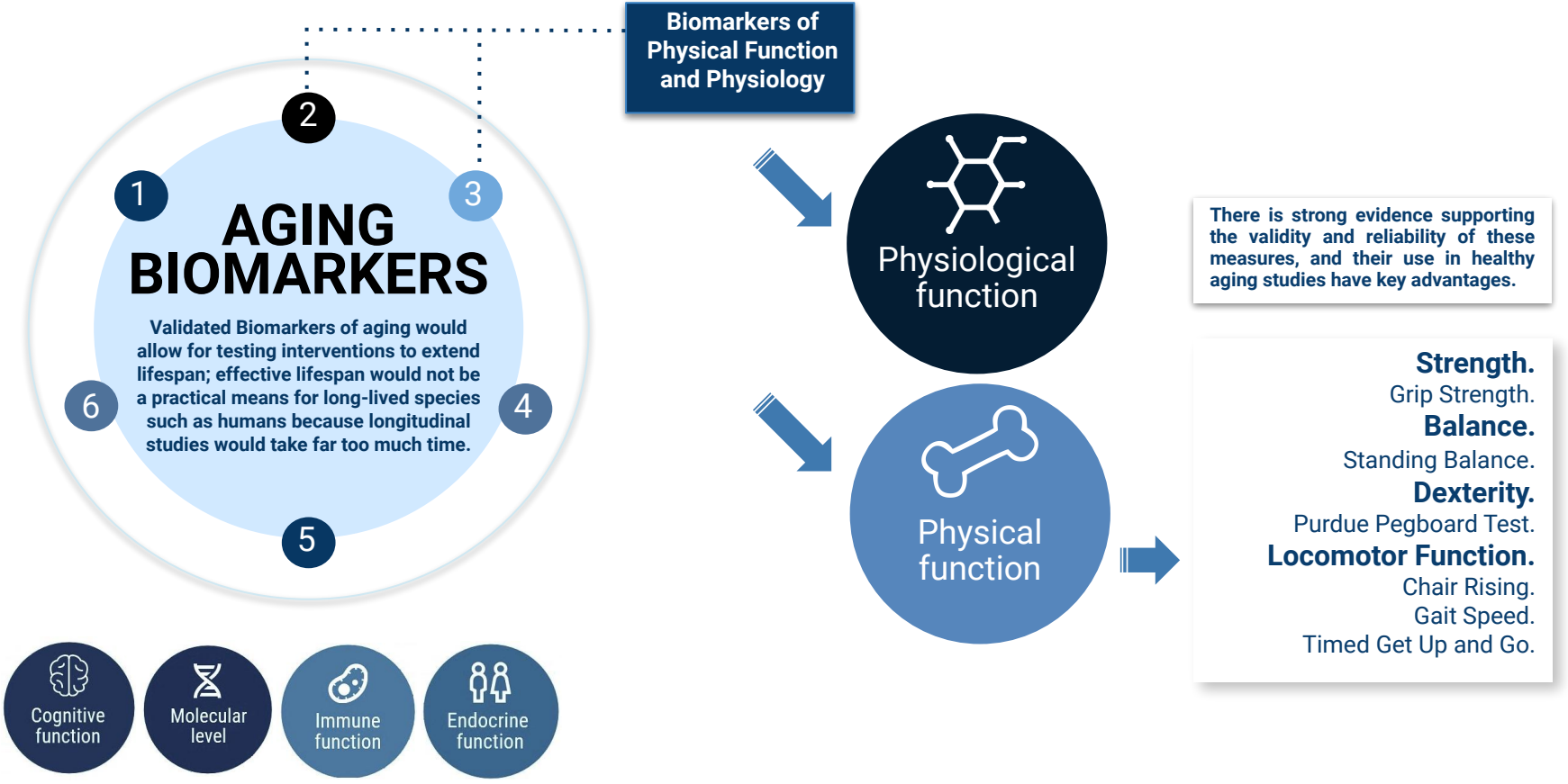
Cardiovascular Function.
*Standard Lipid Profile.
Blood Pressure.
*(Ideally: Advanced Lipoprotein Testing like VAP test).

Lung Function.
FEV1.

Glucose Metabolism.
HbA1C.
Fasting Glucose.
*(Ideally: Skin Autofluorescence Tests like AGE-Reader mu ones).

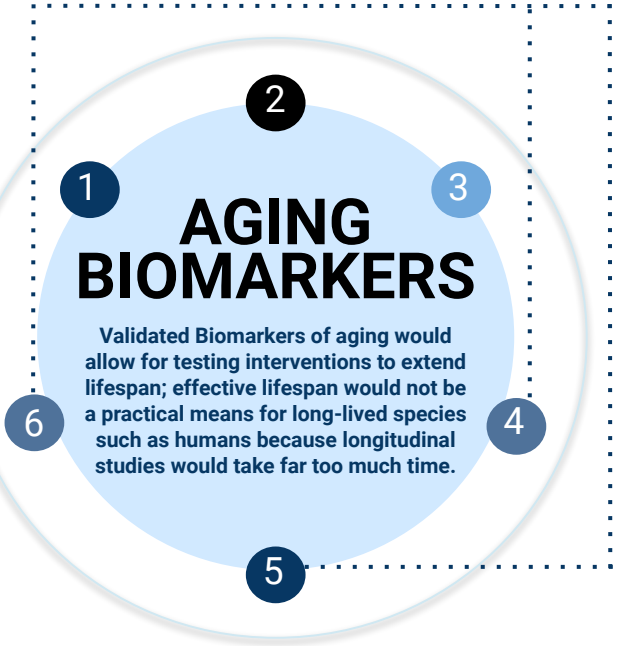
Biomarker Domains Classification Framework.
Biomarkers of Physical Function and Physiology.

AGING ANALYTICS AGENCY



Biomarker Domains Classification Framework.
Blood-based Biomarkers.

AGING ANALYTICS AGENCY



Blood-based Biomarkers

Whilst the field of immunology is well developed, the study of age-related decline in immunity, termed immunosenescence, is more recent. Susceptibility to both bacterial and viral pathogens, incidence of cancer and loss of tolerance to one's own tissues evidenced by increased autoimmunity are clearly related to aging. Studies assessing age-related immune and inflammatory function, including T-cell phenotype, cytomegalovirus serostatus and pro-inflammatory cytokine status (inflammaging), have been the basis for the development of the Immune Risk Profile (IRP).

Immune function

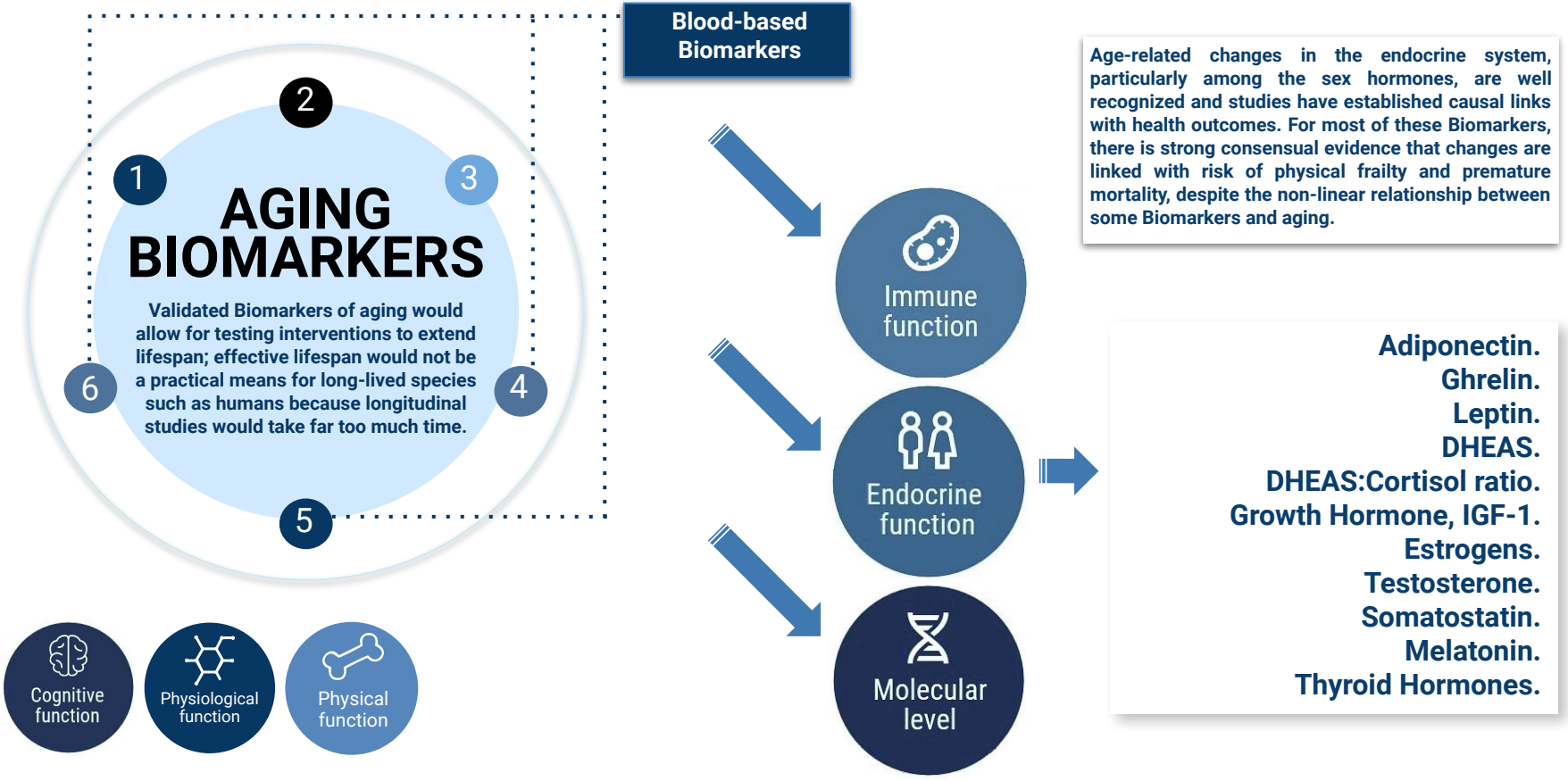
Endocrine function

Molecular level

IRP.
Defined by an inverted CD4/CD8 ratio and associated with increased numbers of CD8 + CD28 cells.

Lymphocyte/Granulocyte ratio.
Neutrophils.
B Cells.
NK Cells.
T Cells phenotype.
Dendritic Cells.
CMV serostatus.
CRP.
Telomere Length in Leukocytes.

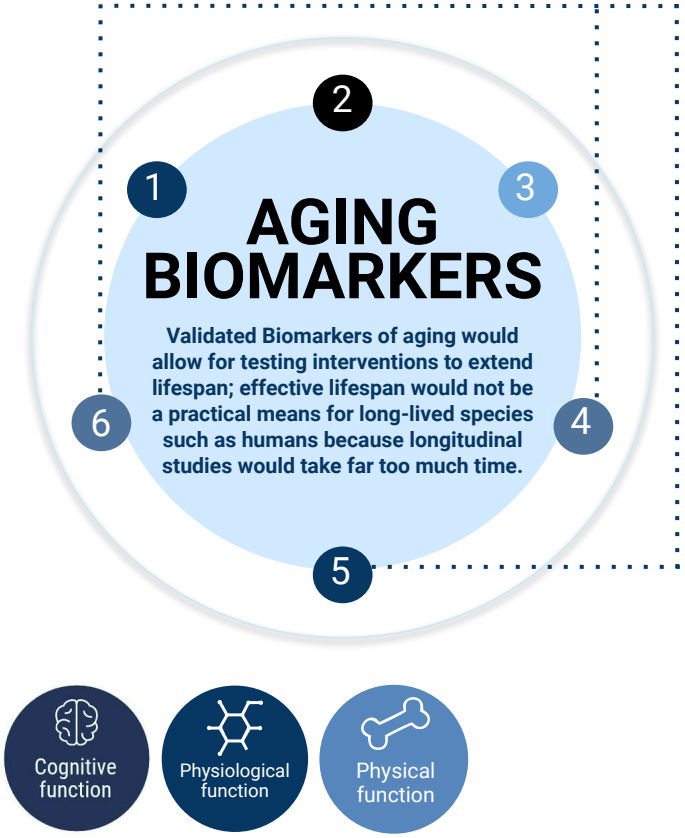
Biomarker Domains Classification Framework.
Blood-based Biomarkers.



Biomarker Domains Classification Framework.
Blood-based Biomarkers.

AGING ANALYTICS AGENCY

Common theories of aging, where age linearly correlates with ROS, DNA damage, mitochondrial dysfunction and shortening of the telomeres, are well established in humans. New approaches contemplate the role of epigenetics, cellular senescence, inflammaging, genomic instability, translational regulation and proteome changes. Taken together, very old humans demonstrate a different picture of aging regarding the accumulation of DNA damage, antioxidant defense capacity, genome instability and telomere shortening by evidenced better DNA repair capacity and higher telomerase activity.



Blood-based Biomarkers

- Immune function
- Endocrine function
- Molecular level

DNA Methylation.
CpGs dinucleotides.

Translational Regulation.
miR-34a.
miR-1, miR-133a, miR-499 and miR-208a.
miR-137, miR-181c, miR-9 and miR-29a/b.

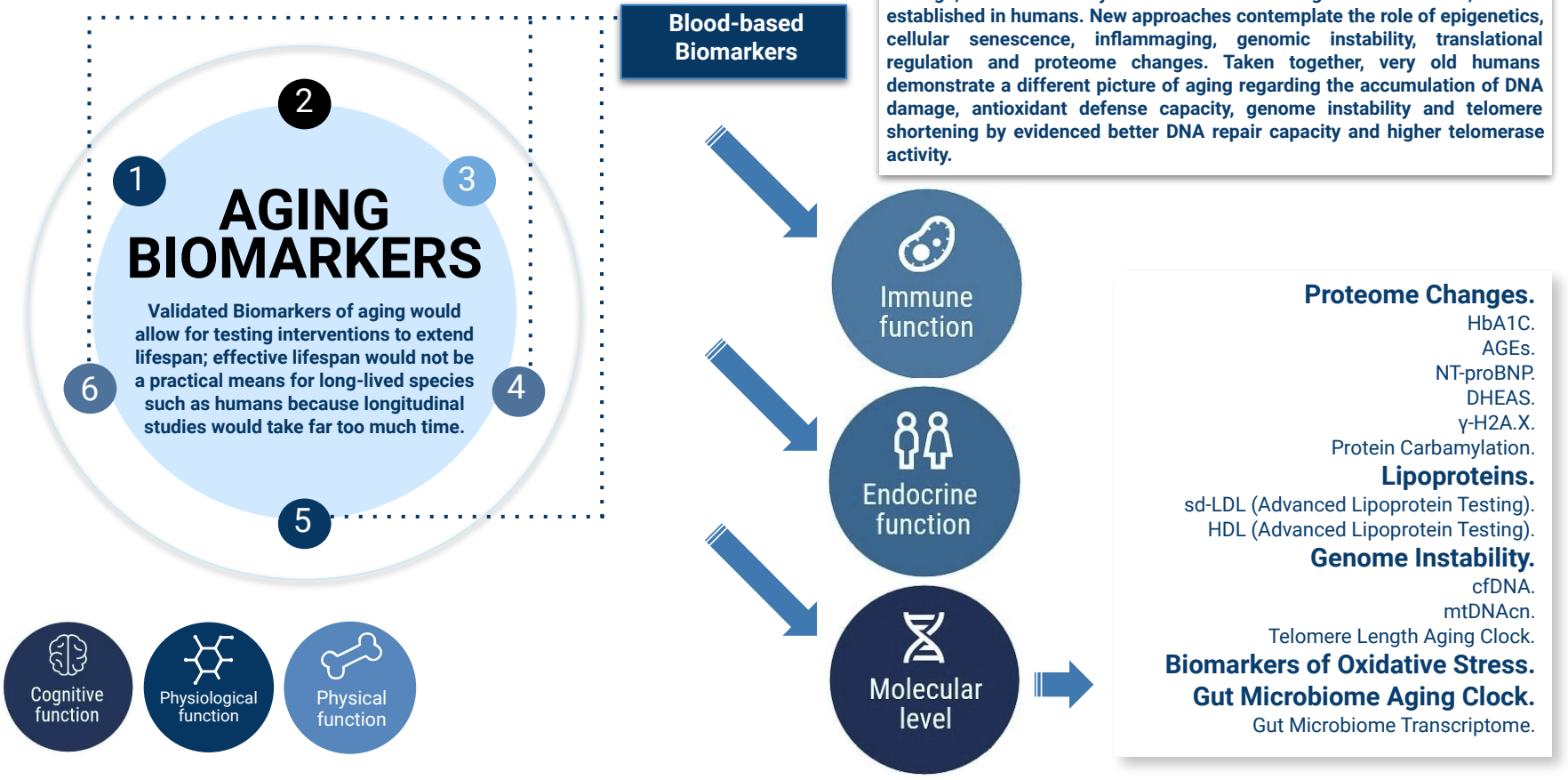
Inflammaging.
IL-1β, IL-6, IL-10, IL-12.
TNF-α.
IFN-γ.
hs-CRP.
Lipoxins.

Cellular Senescence.
β-galactosidase.
p16INK4a.

Biomarker Domains Classification Framework.
Blood-based Biomarkers.

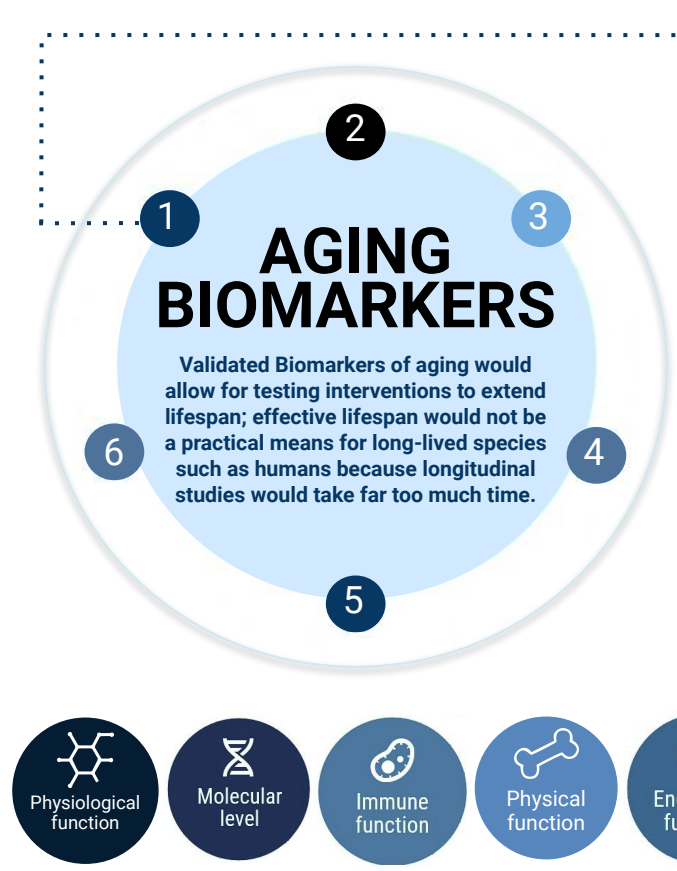
AGING ANALYTICS AGENCY

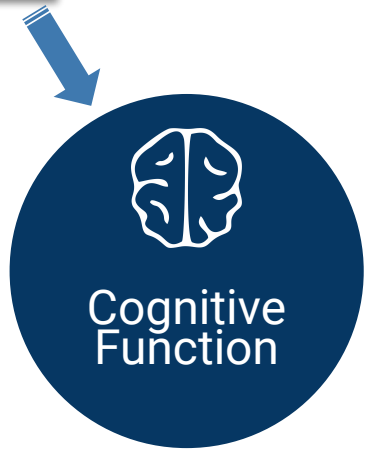
Common theories of aging, where age linearly correlates with ROS, DNA damage, mitochondrial dysfunction and shortening of the telomeres, are well established in humans. New approaches contemplate the role of epigenetics, cellular senescence, inflammaging, genomic instability, translational regulation and proteome changes. Taken together, very old humans demonstrate a different picture of aging regarding the accumulation of DNA damage, antioxidant defense capacity, genome instability and telomere shortening by evidenced better DNA repair capacity and higher telomerase activity.



Biomarker Domains Classification Framework.
Cognitive Biomarkers.

AGING ANALYTICS AGENCY





Cognitive decline is a well documented process common to old age. Structural and function changes in the brain correlate with cognitive decline, including alterations in neuronal structure, neuronal loss, loss of synapses, and dysfunction of neuronal networks. Age-related diseases are directly connected with these processes since they increase the rates of changes at brain level.

Executive Function.
Verbal Fluency.
Processing Speed.
Digit-Symbol Coding.
Working Memory.
Digit Span Backward.
Crystallized Ability.
Boston Naming Test.
Attention.
Stroop Task.
Non-Verbal Reasoning.
Raven's Progressive Matrices.
Visual Memory and Visuospatial Ability.
Benton Visual Retention Test and Block Design Test.
Verbal Memory & Learning
Rey Auditory Verbal Learning Test.

Minimum Required Biomarkers List

AGING ANALYTICS AGENCY

1. Gait (Walking) Speed
2. Timed Get Up and Go
3. Chair Rising
4. Grip Strength
5. Standing Balance
6. Purdue Pegboard Test
7. Spirometry: Forced Expiratory Volume in 1 Second (FEV1)
8. Bone Density, Bone Mass Hip: Dual X Ray Absorptiometry for Bone Health
9. Broadband Ultrasound Attenuation (BUA) at Heel for Bone Health
10. Computed Tomography for Bone Health
11. Dual X Ray Absorptiometry for Estimated Leg Muscle Mass
12. Bioelectrical Impedance Analysis for Muscle Mass
13. Computed Tomography for Muscle Mass
14. Magnetic Resonance Imaging for Muscle Mass
15. Body Potassium for Muscle Mass
16. Abdominal Fat; Waist Circumference
17. Body Mass; Body Mass Index; Body Weight
18. Blood Pressure; Sphygmomanometry
19. Standard Lipid Profile: Total Cholesterol; LDL-C; HDL-C; Triglycerides
20. Glycated haemoglobin (HbA1C)
21. Fasting Plasma Glucose
22. Verbal Fluency
23. Digit-Symbol Coding
24. Digit Span Backward
25. Boston Naming Test
26. Stroop Task
27. Block Design Test
28. Raven's Progressive Matrices
29. Rey Auditory Verbal Learning Test
30. Benton Visual Retention Test
31. Adiponectin
32. DHEAS:Cortisol Ratio
33. DHEAS
34. Growth Hormone; IGF-1
35. Leptin
36. Ghrelin
37. Melatonin
38. Estrogens
39. Somatostatin
40. Testosterone
41. Thyroid Hormones
42. C-Reactive Protein
43. Neutrophils

Most Comprehensive Biomarkers List

AGING ANALYTICS AGENCY

1. B Cells
2. CMV Seropositive
3. Dendritic Cells
4. Natural Killer Cells
5. Lymphocyte/Granulocyte ratio
6. Immune Risk Profile
7. Telomere Length in Leukocytes
8. T Cell Phenotype
9. CpGs Dinucleotides
10. miR-34a
11. miR-1, miR-133a, miR-499 and miR-208a
12. miR-137, miR-181c, miR-9, and miR-29a/b
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18. IL-6
19. IL-10
20. IL-12
21. p16INK4a
22. β-galactosidase
23. Small Dense Low-Density Lipoprotein (sdLDL)
24. High Density Lipoprotein (HDL)
25. AGEs
26. NT-proBNP
27. γ-H2A.X
28. Protein Carbamylation
29. Mitochondrial DNA Copy Number
30. Cell-Free DNA
31. Telomere Length Aging Clock
32. Biomarkers of Oxidative Stress
33. Gut Microbiome Transcriptome

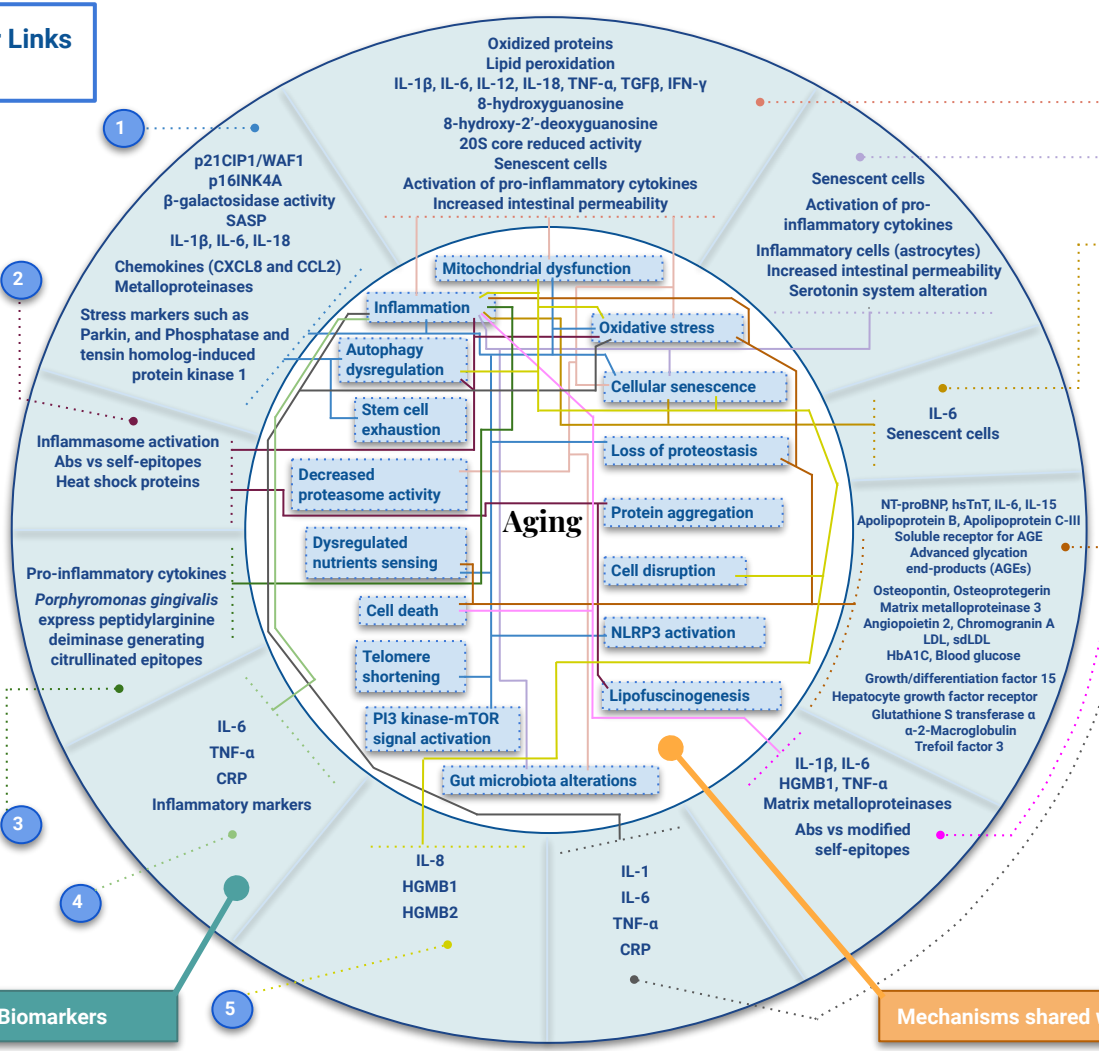
Age-Related Diseases and Molecular Links with Root Causes of Aging.

The longstanding question if old age is itself a disease has been addressed since ancient times, starting from the Roman playwright Terentius, who claimed *senectus ipsa est morbus*, "*old age itself is a disease*", and Cicero who some decades later argued in De Senectute *pugnandum, tamquam contra morbum sic contra senectutem*, "*we have to fight against aging, as we do against a disease*". These quotations elegantly summarize a long-held view of aging and old age addressed by several scholars.

Notwithstanding, with the birth of modern medicine in the nineteenth century, this discussion suddenly ended up in considering aging and diseases as separate phenomena.

Age-Related Diseases, ***Geriatric Syndromes*** and ***Aging itself*** are not separate entities, both should be considered as parts of a continuum and, to support this hypothesis, we at Aging Analytics Agency highlight the meeting points between these phenomena and the need to focus on their basic and shared molecular and cellular mechanisms.

To establish the links between these basic mechanisms shared by ***Aging***, ***Age-Related Diseases*** and ***Geriatric Syndromes***, international experts identified nine pillars or root-causes which actually include adaptation to stress, loss of proteostasis, stem cell exhaustion, metabolism derangement, macromolecular damage, inflammation, epigenetic modifications and senescence, among others. Many chronic diseases and pathological conditions, some of which are considered here, are at least in part determined by (some of) these root-causes or shared mechanisms.



AGING ANALYTICS AGENCY

The Increasing Role of Digital Biomarkers

The continuous monitoring of small changes in health, and the continuous and commensurate micro-adjustment of treatments in response, requires **an agreed panel of biomarkers.** Biomarkers are typically classified as molecules which have properties that allow them to be measured in biological samples in clinical settings. But what if we measure people's health outside the clinic with the help of everyday devices such as a phone?

Thanks to advances in digital technology we now have access to a whole new form of measurable indicator: Digital Biomarkers. Digital Biomarkers are like any other biomarker, but measured through gadgets.

Now we have access to a whole new form of measurable indicator: Digital Biomarkers.

We can measure people's health outside the clinic with the help of everyday devices such as a phone. 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, sensors, implantables and digestible devices.

"Digital" expresses the data collection methodology as using sensors and computational tools, and across multiple layers of hardware and software. This data can be used not only to confirm the presence of any kind of disease but to predict and, moreover, prevent all possible pathologies.

A currently in development Digital Biomarker of aging that also use Deep Learning-driven analysis, for instance, involve the aggregation of photographs continuously taken to mice under the MouseAGE Project; these images associate behavior and other traits with a biological age endpoint. These also can be quite easily extended to humans and similar developments are taking place, involving algorithms designed to operate from mobile phone applications or wearable devices. The precision of this electronic devices alone is still not enough to make these implementations a research priority, but the increasing video capabilities of smart-phones means that the accelerated developments in Digital Imaging Biomarkers (e.g., for the face or eye, collecting data about ocular or neurological diseases) may be implemented sooner rather than later.

The Increasing Role of Digital Biomarkers

Quantified in ones and zeros, the Digital Biomarkers or their related Digital Panel Platforms can support continuous measurements outside the physical confines of the clinical or the hospital environment, using home-based connected products. These products have created new opportunities, enabling remote monitoring for biomedical research, decentralized clinical trial designs, and routine patient care. These are components already well integrated into the market, but still waiting to be used to good advantage by the world's health systems.

Nowadays Digital Biomarkers are widely studied in order to reveal the broad spectrum of possible uses, and to revolutionize current methods of patient health state monitoring and disease outcomes prediction. According to **Digital Biomarkers Journal**, a multidisciplinary-by-design open access journal that bridges the disciplines of computer science, engineering, biomedicine, regulatory science and informatics, Digital Biomarkers represent an opportunity to capture clinically meaningful, objective data.

Digital Biomarkers could be the breakthrough bioscience has been waiting for, which is why not only individuals and health care providers but also many companies have grabbed the opportunity with both hands. Breathometer, Xsensio, Scailyte AG, Nightingale Health, FEET ME, xbird, Mindstrong Health, Serimmune, IXICO, etc., are top private companies that successfully carry out the mission of Digital Biomarker popularization. They are known for the development of unique sensing platforms and chips, human liquid testing systems, devices for health monitoring, single-cell profiling devices, and providing unique information that fuels development of new diagnostics, vaccines, and therapeutics. All of these enable novel approaches for preventing and treating a great many diseases; not only pathologies and conditions of aging, but the vast majority associated without any doubt with age and Longevity.

Digital Biomarkers span a broad range of preventive, diagnostic and prognostic measurements, with opportunities and challenges associated with their use. Some Biomarkers are immediately familiar to patients or physicians as they are digitized versions of well-established metrics—for example, glucometer readings transmitted by Bluetooth, or the timed six-minute walk test measured with the smartphone's built-in gyroscope and accelerometer. Others, such as the smartphone-derived tapping test for Parkinson's disease severity, are entirely novel and evolving. They are able to detect eye diseases from scans as accurately as experts, or to predict patient deterioration up to 48 hours earlier than currently possible, developments carried out by DeepMind Technologies, now belonging to Alphabet. Also, Digital Biomarkers can be components in autoregulated closed loop systems; for instance, a continuous glucose sensor linked to an insulin pump in a pancreas can automatically dose or micro-dose insulin in patients with diabetes.

Developing and adopting safe and effective digital biomarkers to improve patient outcomes.

AGING ANALYTICS AGENCY

Category (a)	Definition (a)	Example (a)	Corresponding Digital Biomarker Examples
Susceptibility/Risk Biomarker	A biomarker that indicates the potential for developing a disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.	Breast Cancer genes 1 and 2 (BRCA1/2) mutations may be used as a susceptibility/risk biomarker to identify individuals with a predisposition to develop breast cancer.	[*] Detect cognitive changes in healthy subjects at risk of developing Alzheimer's disease using a video game platform. **Source:** *Gold, M. et al. Digital technologies as biomarkers, clinical outcomes assessment, and recruitment tools in Alzheimer's disease clinical trials. Alzheimers Dement. 4, 234–242 (2018).*
			[**] Classify adults at high risk of late-onset Alzheimer's disease using computerized cognitive testing. **Source:** *Ritchie, K. et al. The midlife cognitive profiles of adults at high risk of late-onset Alzheimer's disease: the PREVENT study. Alzheimers Dement. 13, 1089–1097 (2017).*
			[*] Reduce key risk metrics for anterior cruciate ligament injury during jump landings using inertial sensor-based feedback. **Source:** *Dowling, A. V., Favre, J. & Andriacchi, T. P. Inertial sensor-based feedback can reduce key risk metrics for anterior cruciate ligament injury during jump landings. Am. J. Sports Med. 40, 1075–1083 (2012).*
Diagnostic Biomarker	A biomarker used to detect or confirm the presence of a disease or condition of interest or to identify individuals with a subtype of the disease.	Repeated blood pressure readings obtained outside the clinical setting in adults 18 years and older may be used as a diagnostic biomarker to identify those with essential hypertension.	[*] Diagnose ADHD in children using eye vergence metrics. **Source:** *Varela Casal, P. et al. Clinical validation of eye vergence as an objective marker for diagnosis of ADHD in children. J. Atten. Disord.*
			[*] Detect arrhythmias using convolutional neural networks and a wearable single-lead heart monitor. **Source:** *Rajpurkar, P., Hannun, A., Masoumeh, H., Bourn, C. & Ng, A. Cardiologist-level arrhythmia detection with convolutional neural networks. arXiv preprint arXiv:1707.01836*
			[*] Detect depression and Parkinson's disease using vocal biomarkers. **Source:** *Gosh, S. S. & Ciccarelli, G. Speaking one's mind: vocal biomarkers of depression and Parkinson disease. J. Acoust. Soc. Am. 139, 2193 (2016).*
			[*] Diagnose asthma and respiratory infections using smartphone-recorded cough sounds. **Source:** *RespApp. Diagnosing Respiratory Disease in Children Using Cough Sounds 2 (SMARTCOUGH-C-2).*

Developing and adopting safe and effective digital biomarkers to improve patient outcomes.

AGING ANALYTICS AGENCY

Category (a)	Definition (a)	Example (a)	Corresponding Digital Biomarker Examples
Monitoring Biomarker	A biomarker measured serially for assessing the status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent.	Prostate-specific antigen (PSA) may be used as a monitoring biomarker when assessing disease status or burden in patients with prostate cancer.	[**] Monitor signs of Parkinson's disease using smartphone-based measurements. **Source:** *Sage Bionetworks. Sage Bionetworks in Collaboration with The Michael J. Fox Foundation Announce Winners in the DREAM Parkinson's Disease Digital Biomarker Challenge.*
			[*] Quantify Parkinson's disease severity using smartphones and machine learning. **Source:** *Zhan, A. et al. Using smartphones and machine learning to quantify Parkinson disease severity: the mobile Parkinson disease score. JAMA Neurol. 75, 876–880 (2018).*
			[**] Track time and location of short-acting beta-agonist inhaler use using an attached wireless sensor. **Source:** *Barrett, M. A. et al. Effect of a mobile health, sensor-driven asthma management platform on asthma control. Ann. Allergy Asthma Immunol. 119, 415–421 (2017).*
			[*] Predicting sleep/wake patterns from a 3-axis home-based accelerometer using deep learning. **Source:** *Wolz, R., Munro, J., Guerrero, R., Hill, D. L. & Dauvilliers, Y. Predicting sleep/wake patterns from 3-axis accelerometry using deep learning. Alzheimer Dement. 13, P1012 (2017).*
			[*] Detection of nocturnal scratching movements in patients with atopic dermatitis using accelerometers and recurrent neural networks. **Source:** *Moreau, A. et al. Detection of nocturnal scratching movements in patients with atopic dermatitis using accelerometers and recurrent neural networks. IEEE J. Biomed. Health Inform. 22, 1011–1018 (2018).*
Prognostic Biomarker	A biomarker used to identify the likelihood of a clinical event, disease recurrence, or progression in patients who have the disease or medical condition of interest.	Increasing prostate-specific antigen (PSA) may be used as a prognostic biomarker when evaluating patients with prostate cancer during follow-up, to assess the likelihood of cancer progression.	Stratify mental health conditions and predict remission using passively collected smartphone data. **Source:** *Mindstrong Health. Mindstrong Health and Takeda Partner to Explore Development of Digital Biomarkers for Mental Health Conditions (2018)*
			Detect post-acute care deterioration in patients at home, applying machine learning to multi-sensor digital ambulatory monitoring. **Source:** *physIQ (http://www.physiq.com/resources/)*

Developing and adopting safe and effective digital biomarkers to improve patient outcomes.

AGING ANALYTICS AGENCY

Category (a)	Definition (a)	Example (a)	Corresponding Digital Biomarker Examples
Predictive Biomarker	A biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent.	Human leukocyte antigen allele (HLA)–B*5701 genotype may be used as a predictive biomarker to evaluate human immunodeficiency virus (HIV) patients before abacavir treatment, to identify patients at risk for severe skin reactions.	Predict autism risk in the siblings of children with autism, using an EEG biomarker. **Source:** *Bosl, W. J., Tager-Flusberg, H. & Nelson, C. A. EEG analytics for early detection of autism spectrum disorder: a data-driven approach. Sci. Rep. 8, 6828 (2018).*
			Detect asymptomatic atrial fibrillation (AF) as a stroke risk factor, remotely through a connected device. **Source:** *Halcox, J. P. J. et al. Assessment of remote heart rhythm sampling using the AliveCor Heart Monitor to screen for atrial fibrillation: The REHEARSE-AF Study. Circulation 136, 1784–1794(2017).*
Pharmacodynamic /Response Biomarker	A biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent.	Blood pressure may be used as a pharmacodynamic/response biomarker when evaluating patients with hypertension, to assess response to an antihypertensive agent or sodium restriction.	Measure cognitive performance with the Cambridge Neuropsychological Test Automated Battery (CANTAB) to test the effects of erythropoietin. **Source:** *Kessing, L. V. Effects of Erythropoietin on Cognition and Neural Activity in Bipolar Disorder (PRETEC-EPO). https://clinicaltrials.gov/ct2/show/NCT03315897 (2017).*
			Measure blood pressure using a digital sphygmomanometer to assess response to antihypertensive therapy. **Source:** *Padwal, R. S. Validation of the Omron HEM-9210T by the ANSI/AAMI/ISO 81060-2 with two novel cuffs: wide range and extra-large. Blood Press Monit. 22, 379 (2017).*

(a) Selected from the FDA-NIH "Biomarkers, EndpointS, and other Tools" (BEST) classification for traditional biomarkers
[*] Digital biomarker under development
[**] Digital biomarker in use (in a clinical trial or an FDA cleared/approved digital health product, or a digital health app in use not requiring approval)

Sources Coravos A., et al. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. *2019.*

Digital Biomarkers, Pharma Industry, Translational Medicine and P4 Medicine.

Digital Biomarkers could potentially reorganize the whole pharma industry and become an integral part of the drug development process. Due to the sensitivity and precision they provide, digital biomarkers can be used to improve clinical trials of drugs. While testing a treatment, finding the appropriate dosage, and looking for side effects, this new form of indicator reveals a drug's efficacy and toxicity for individual patients.

In 2017 the **Digital Biomarkers Journal** provided a deep analysis of the modern pharmaceutical business model and how it implements digital biomarkers. According to the article, in the case of some illnesses, Digital Biomarkers can improve the understanding of the natural history of a disease through more continuous measurement of objective health data. Such information may become priceless in situations where symptom presence and severity is more variable and disease prevention and treatment necessitates a more individualized approach to each patient.

As Digital Biomarkers are increasingly used as endpoints in drug discovery and development, translational research and clinical trials, we anticipate that clinicians will have a growing number of validated means of gathering deep insights on patients health status remotely. Digital Biomarkers allow deep collection of data on individual trial participants as well as patients in clinical settings, thereby providing an opportunity for “N of 1” clinical investigations, the cornerstone of evidence generation for personalization of care. And with more data, an algorithm’s accuracy improves. This strong feedback between massive amounts of data and improvement of interpretive algorithms is sufficient to consider that the amplitude levels of the Digital Biomarkers and the Digital Panel Platforms are much higher than those of conventional biomarkers and panels - and will be even more, as the latter join one by one to this emerging system, establishing a new paradigm of daily overall health assessment. This will trigger excessive accuracy in the measurement of biomarkers; process that is already underway and can be seen in multiple market-ready products, such as the AgeMeter, developed by Centers for Age Control, a functional or biological age test system using digital health inputs for improve personalized health parameters.

Availability of contextual information will enable more precise personalized algorithms, as a blood pressure fluctuation algorithm designed for a population with a late-stage cardiovascular disease, and also providing opportunities to combine data sources to create novel measures for conditions that have historically struggled to have meaningful endpoints, as the brain and nervous system disorders. Nevertheless, validation of digital biomarkers require a uniquely collaborative effort, with translational science, engineering, data science and health information technology functions tightly coordinated as a highly integrated multidisciplinary unit.

Digital Biomarkers, Pharma Industry, Translational Medicine and P4 Medicine.

As previously stated, there are many examples of Digital Biomarkers in use or actively under development today, as well as computational algorithms with potential for development into Digital Biomarkers. The time is now to give forethought to strong incentive structures to promote the safe and effective use of Digital Biomarkers. The verification and validation of a Digital Biomarker should be not construed as a one-time process, but rather, a learning digital health system should continuously collect data and handle modifications and updates over time.

Industry, researchers, policy regulators, clinicians, and patients have a joint responsibility to design such a learning system that can improve Digital Biomarker products, empower patients, and improve global health and healthcare delivery for everyone. That is the challenge, and the opportunity.

Personalization and precision of diagnostics, prognostics and treatment for individual patients

AGING ANALYTICS AGENCY

Healthy lifespan extension and ageing processes reversal to a young state

01 Access to advanced preventive restorative medicine technologies

- Safe testing of novel therapies on individual`s stem cells, skin and other organs

02 Personalized Longevity programs

- Personalised diagnostics, prognostics and therapeutics
- Virtual human body for health monitoring

03 Health management by world leading experts

- Continuous health monitoring by the world leading experts

Sources: Coravos A., et al. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. *2019.*

Preventive Treatment

This eclectic range of biotechnologies owe their "preventive medicine" status to the fact that each can be applied (and micro-adjusted) in response to continuous monitoring of Biomarkers.
In order to achieve an optimal panel of aging Biomarkers for precision prevention, diagnosis, treatment and prognosis, data must be taken using multiple health variables from people who are not currently patients. This is an almost entirely impractical task to do manually; automated platforms have already loaded the future, they will be the environment of the massive and deep data flow; artificial intelligence is revealing the fine reticular patterns that will give sense and actionability to that future; frontier technology and treatments, awaiting for clinical validation but almost market-ready, are the skilled and precise hand that will deliver radical prolongation of health and wellness to the societies of the next decade and the economies that guide their efforts to remain competitive and at the forefront of the next Biggest and Most Complex industry in human history.

Early pre-symptomatic preventive intervention

- Gene therapies
- Cell therapies
- Tissue engineering
- Small molecules and biologics

- Natural mimetics of validated geroprotectors (e.g. metformin, rapamycin)
- Genetically engineered cell therapies
- 3D bioprinting
- Microbiome engineering

Digital Avatar - Virtual You

What is an Avatar?

An avatar is a graphic representation that is associated with a user to serve as their identification. Avatars can be a picture, artistic drawing, or a three dimensional representation. With the advent of the digital revolution, its use has spread to a large number of fields including medicine. Currently, the digital avatar is being used in medical education such as for training models using augmented reality in order to explain anatomy to students with a three-dimensional human body.

A good example for its usefulness within the context of health is the projection of the effects of tobacco in a patient who is a smoker, which allows us to visualize their body within 5 years and analyze the consequences to their health in the near future if they continue to smoke. The challenge is keeping in mind the quantity of information that exists regarding pathological conditions and the consequences. How can we motivate people to adopt good habits? The digital avatar in health allows us to plan a path and observe the body of a patient in alternate scenarios.

A virtual profile of all health data can be generated through collection of multiple types of data, some of which are visualised also in 3D through devices or augmented reality. Biomarkers serve not only to diagnose issues, but also to evaluate overall health status and predict aging rates of each individual. Gathering more of this type of data e.g. periodic blood tests, will enable a complex, highly personal picture of each person, whose predictive power will be proportional to the quantities of input classes and the intrinsic capabilities of the AI-driven analysis aimed at recreating biomarker networks. The added accuracy and size of the data sets means it will inevitably provide an invaluable source for AI to pick out key trends for each kind of patient cohort, or indeed work out the cohorts itself.

Despite being a trove of knowledge for health practitioners and researchers, individuals will still be the sole proprietors of their own health data, allowing them to control who sees what, and how this data is used for various monetisation purposes. This is enabled by blockchain storage of patient data. In addition to biomarkers, all other types of data relevant to healthcare will be integrated into the digital avatar. Health records, medication, lifestyle will be fed into the profile. The ability to process patient data on a bigger scale compared to traditional medicine enables truly personalised healthcare, and removes the difficulties of identifying individual patient backgrounds and needs, that doctors may fail to obtain in time. With the technologies of healthcare advancing, the digital avatar will evolve from a data collection and disease focused tool to a truly longevity focused tool. Instead of looking at unidimensional, disease-linked biomarkers, it will be able to look at the whole organism in an overarching health point of view, and focus mainly on prevention and extending patient healthspan.

Sources: Digital Health. Fundación Innovación Bankinter.

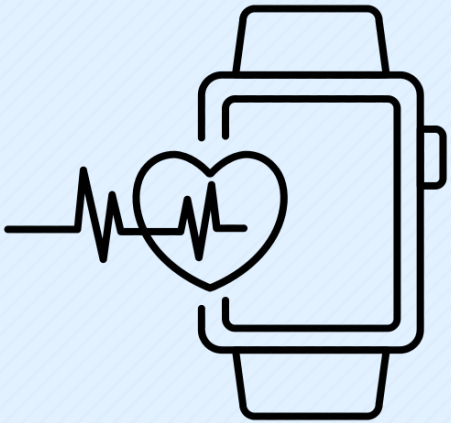
The Anatomy and Evaluation of Digital Biomarkers

Measurements

An input layer such as a camera, microphone, or sensor captures a digital biomarker signal. For example, photoplethysmographs measure blood volume changes in the microvasculature using an optical sensor placed on the skin surface. A signal processing layer, typically an algorithm, converts the input signal into actionable metrics (e.g., oxygen saturation and/or heart rate), or digital biomarkers. Although measuring blood volume changes using photoplethysmography is widely accepted in medical practice, the interplay among hardware, sensors, and algorithms can make the evaluation of emerging digital biomarkers difficult. There are several challenges in deciding not only whether a digital biomarker is valid, but equally important, whether it is "fit-for-purpose", meaning that the product has an explicit context of use, meets appropriate requirements for accuracy and precision, and is accompanied by the metadata needed for analysis and interpretation.

Verification

Analytical verification uses engineering bench tests to ensure that the product is measuring and storing values accurately by confirming the tool's accuracy, precision, and reliability. Confidence in the performance of digital biomarkers is an important consideration for researchers, clinicians, and patients. For example, the verification step ensures that the translation from raw data, e.g., that a heart rate sensor measuring electrical potential in millivolts, faithfully converts that signal into an accurate heart rate, expressed in beats per unit of time.



Validation

As with diagnostics, the performance of digital biomarker algorithms may vary across different patient populations, producing different rates of false-positive or false-negative outputs in different groups. Validation addresses whether the measurement is applicable in the target population and context of use,6 which would render digital biomarker "fit for purpose". For example, a tool measuring sleep and waking periods perform against polysomnography may perform differently in a patient population with insomnia versus sleep apnea versus healthy volunteers.

Sources: Andrea Coravos, et al. Developing and adopting safe and effective digital biomarkers to improve patient outcomes. *2019.*

Biomarkers of Physical Function and Physiology

Biomarkers of Physical Function Domain Overview

Measures of physical capability, that is, a person's ability to perform the physical tasks of everyday living, are useful markers of current and future health. Poor performance in tests of grip strength, walking speed, chair rise time and standing balance, and so on, are associated with higher mortality rates. In addition, lower levels of physical capability are associated with higher risk of cardiovascular disease (CVD), dementia, institutionalisation and difficulties performing activities of daily living (ADLs). Locomotor function, strength, balance and dexterity, are considered to capture underlying functions that are used most commonly as objective measures of physical capability in longitudinal studies.

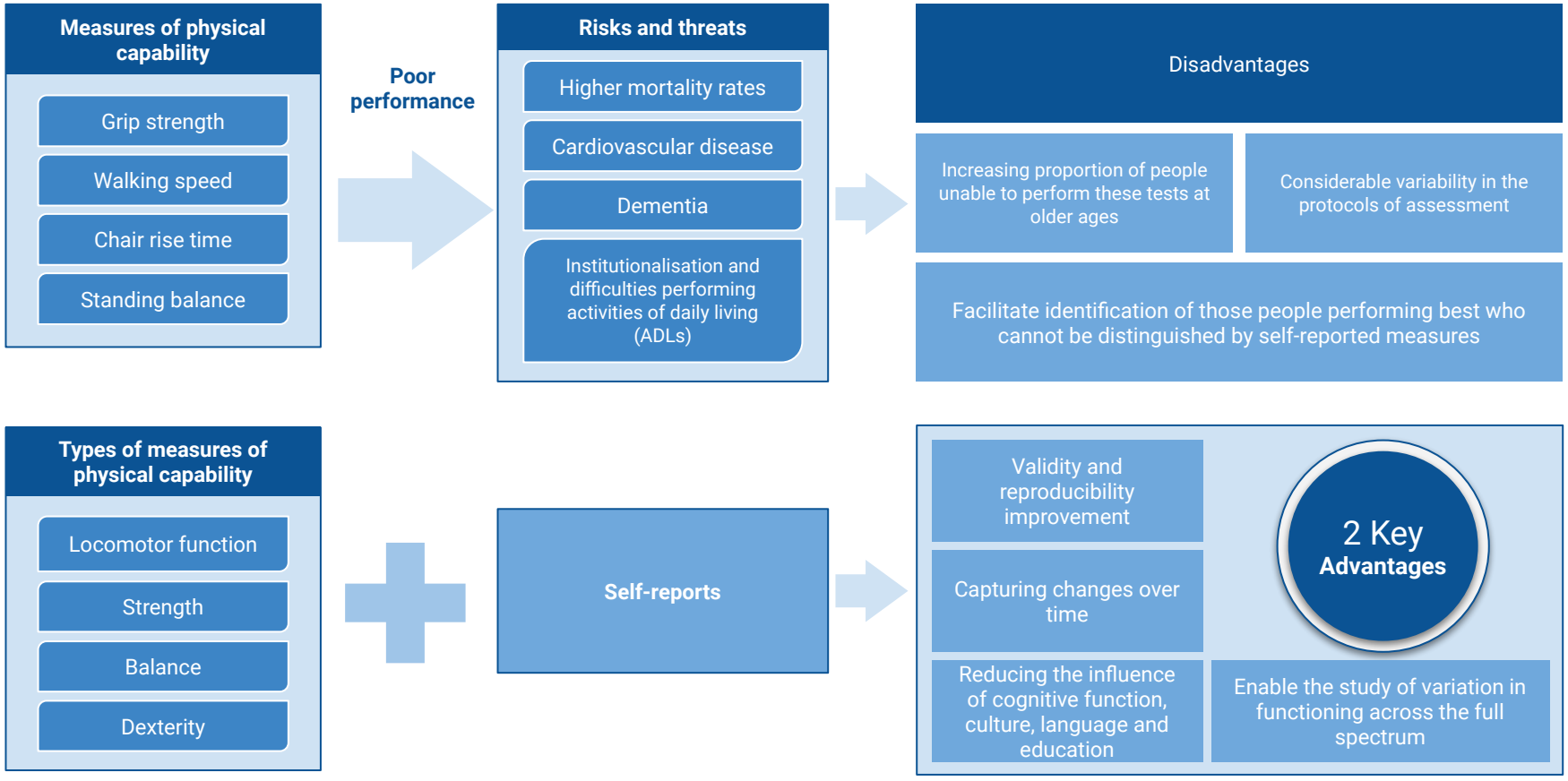
Objective, standardised tests of physical capability have been developed and are used increasingly in population-based studies. These objective measures complement self-reports, improve validity and reproducibility, capture change over time, and may reduce the influence of cognitive function, culture, language and education that can affect self-reported assessments and so limit comparability across studies. From the perspective of healthy ageing, these objective tests have two key advantages. Firstly they enable the study of variation in functioning across the full spectrum. Secondly, they facilitate identification of those people performing best who cannot be distinguished by self-reported measures which aim to identify people who have difficulty in performing the tasks of everyday living.

There is considerable variability in the protocols of assessment for these measures, but attempts at standardisation across studies are now being made through initiatives such as the NIH toolbox [intro]. All tests of physical capability are relatively quick, easy and inexpensive to perform with only grip strength and the pegboard test requiring special instruments. An exception is the use of an accelerometer to measure swaying during balance tests which is recommended by the NIH toolbox. There is strong evidence supporting the validity and reliability of these measures.

However, all the physical capability tests have exclusion criteria and an important consideration, not well addressed in the literature, is how to handle the increasing proportion of people unable to perform these tests at older ages. Grip strength is the most comprehensively studied physical capability test. Longitudinal studies show that grip strength peaks in the late thirties for both sexes, while longitudinal and cross-sectional studies show declines in both sexes from the fifties and sixties. At all ages, grip strength is higher in men than women and there is some evidence for faster decline in men than in women.

Sources: Jose Lara, et al. A proposed panel of biomarkers of healthy ageing. *2015.*

Biomarkers of Physical Function Domain Overview



Biomarkers of Physical Function Domain Overview

Evidence for age-related change in other measures of physical capability is more limited because it is restricted largely to cross-sectional data from relatively small studies. However this limited evidence is consistent in suggesting that physical capabilities decline progressively in later life and that men perform better than women at all ages.

A systematic review has shown that weaker grip strength, slower walking speed, longer chair rise time and poorer standing balance performance are associated with higher mortality rates, independent of age in older community-dwelling populations. Meta-analyses of data from several American studies of older people have also revealed a strong association between slower walking speed and higher mortality rates. More recent studies indicate that, in addition to grip strength and walking speed, standing balance and chair rise speed in middle age predict mortality rates over 13 years of follow-up.

In another recent systematic review, weaker grip strength was found to be associated with functional decline as assessed by self-reported difficulties performing activities of daily living (ADLs). Three other systematic reviews evaluating risk for subsequent disability (assessed using ADLs) showed that older adults performing poorly in tests of physical capability are more likely to become disabled.

There is also some evidence that poorer performance in grip strength, walking speed, chair rise times and standing balance, is associated with higher risk for cardiovascular disease (CVD), dementia and institutionalisation (as a marker of loss of independence), but none of these associations has been studied sufficiently often to allow definitive conclusions to be drawn.

Higher mortality rates prediction

- Weaker grip strength
- Slower walking speed
- Longer chair rise
- Poorer standing balance performance

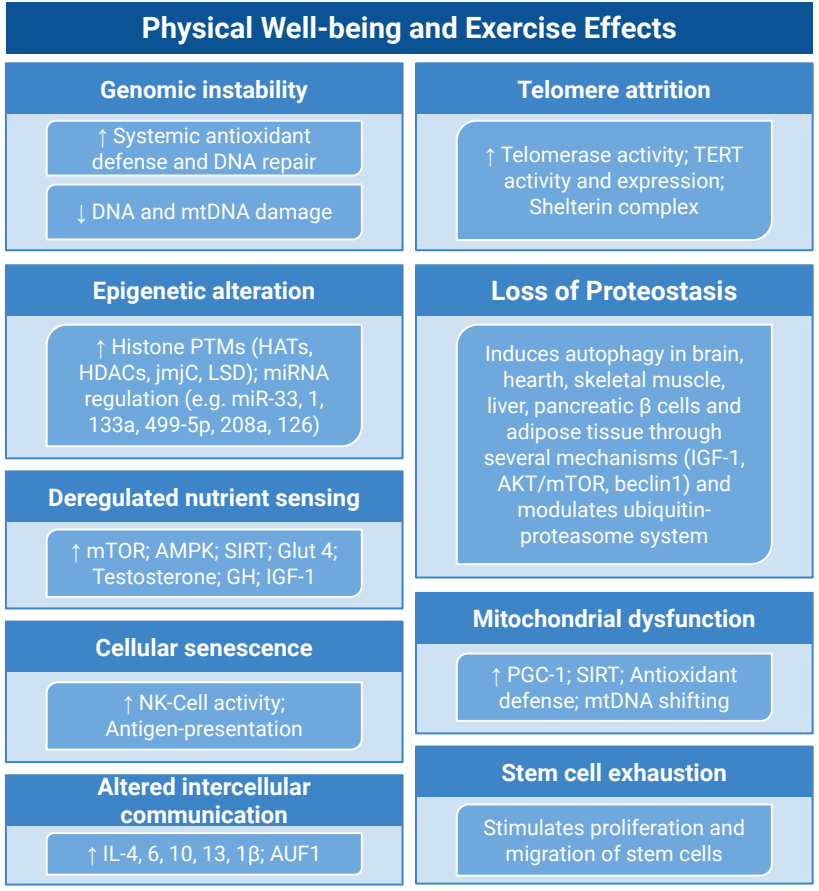
Weaker grip strength was found to be associated with functional decline as assessed by self-reported difficulties performing activities of daily living (ADLs)

Older adults performing poorly in tests of physical capability are more likely to become disabled

Weaknesses in the Physical Function Biomarker Domain

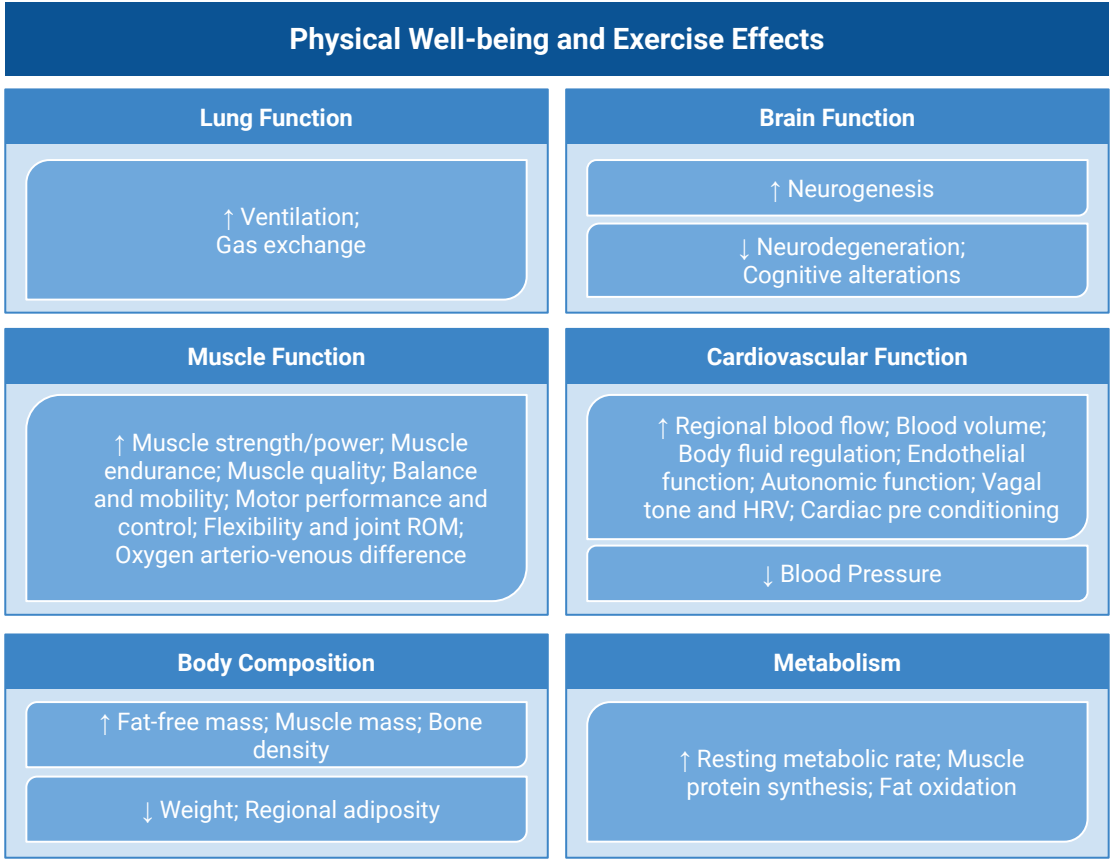
Recent work suggests that there is added value, for the prediction of mortality, in assessing different measures of physical capability in midlife. However, there is currently insufficient evidence, from the perspective of studying healthy aging, to establish the added value of assessing any one additional specific measure, if other measures have been assessed already, to recommend an order of priority for these measures or to define with confidence the minimum number of measures that should be made across the full range of older ages and for different research questions. Some studies consider each measure of physical capability separately, and some have used a set of tests of several aspects of physical capability interpreted as a total performance score, such as the short physical performance battery (SPPB) or the index of physical fitness age. Further work should establish whether deriving an overall score of physical capability is of greater predictive value than considering each measure separately and the most appropriate approach is likely to depend on the specific research question being addressed.

There is a need for more studies with longitudinal data on change in physical capability, and a need to assess physical capability in relation to other positive aspects of health, such as quality of life, that may be important criteria for healthy aging. Significant variability in the protocols used to assess any one measure of physical capability makes comparisons between, and combination of findings from, different studies difficult. In addition, few studies have compared formally the different measures of physical capability and, as with measures of cognitive function, performance in any one measure of physical capability is likely to be correlated with performance in other such measures.



Weaknesses in the Physical Function Biomarker Domain

There is also a need for larger longitudinal studies in which these age-related patterns, as well as variations in within-individual changes over time, can be investigated further. Declines in mean levels of physical capability at the population level hide substantial inter-individual variation in rate of decline. For example, being able to identify people who maintain, or improve, their physical capability despite increasing age will be important when studying healthy aging. More research is also needed on the utility of some measures such as dexterity performance in the pegboard test (dexterity), which has been understudied; this in addition to the aforementioned dearth of evidence on the associations of physical capability with measures of positive aspects of health that may be important criteria for healthy aging.



Biomarkers of Physiology Domain Overview

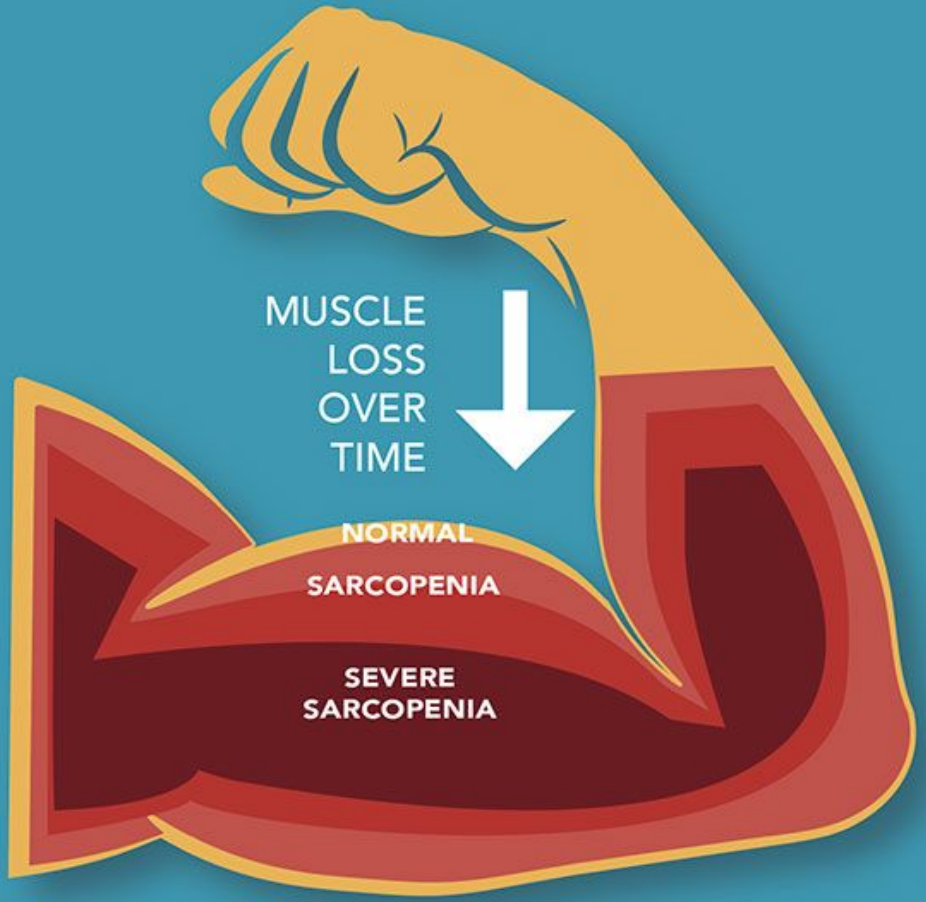
Complex molecular changes affecting the structure and function of most cells, tissues and organ systems are a hallmark of aging, and changes in their function can be detected by the third or fourth decades of life. Such loss may translate, eventually, into metabolic dysregulation leading to the development of early signs of pre-disease which, if not identified and managed, will result eventually in functional loss, chronic disease and finally death. A well-recognised example is age-related loss of skeletal muscle mass and strength potentially leading to sarcopenia. However, subtle changes in the function of most organs can occur by the third or fourth decades of life.

This domain includes biomarkers of lung function, body composition (including bone mass and skeletal muscle), cardiovascular (CV) function and glucose metabolism.

Body mass and body composition. Aging is associated with body composition changes including increased body fat, reduced muscle mass and, with exception of the heart, reduced organ mass. Greater abdominal adiposity is a risk factor for aging and for age-related diseases with the lowest mortality risk for those with waist circumferences (WC) below 94 and 77 cm for men and women, respectively. The relative risk (RR) of mortality is doubled for those with WCs above 132 and 116 cm in men and women, respectively.

Body mass index (BMI) is a useful measure of overall adiposity, since each 5 kg/m2 Increase in BMI is associated with 30% higher overall mortality, 40% higher vascular mortality, 60–120% higher diabetic, renal, and hepatic mortality. High BMI, independent of gender and other confounding factors, is a risk factor for cognitive decline. In addition, weight gain in middle age is associated with substantially reduced likelihood of healthy survival after age 70 years in women.

Muscle mass can be assessed using CT, magnetic resonance imaging (MRI), DXA, bioimpedance analysis (BIA), and body potassium. Evidence shows that muscle mass, such as leg muscle mass, declines with age. Cross sectional and prospective studies that have examined the relationship between regional muscle mass per se and health outcomes have reported that low skeletal muscle index (skeletal muscle mass/body mass percent) is associated with increased likelihood of functional impairment and disability. Recent developments from the FNIH Sarcopenia Project may help to establish universal cut-points for low muscle mass and weakness.



30 Million
Undiagnosed/
Unaware

88% of Adults
55+ at
Risk for
Sarcopenia

18 Million
have been
clinically
diagnosed

Sarcopenia is
preventable,
reversible and
treatable
without
medication.

Biomarkers of Physiology Domain Overview

Cardiovascular function. Aging of the cardiovascular system is associated with aging of both cardiac muscle and the vascular wall. Although there are many inflammation and haemostasis-related biomarkers of cardiovascular function, the classical, widely measured, and well documented physiological markers of risk of cardiovascular-related diseases remain the strongest biomarkers of aging. Systematic reviews and meta-analyses provide strong evidence that blood pressure (BP), lipid profile (including total cholesterol, low- and high-density lipoprotein cholesterol, and triglycerides concentrations) are predictors of morbidity and mortality. A difference of 20 mmHg in systolic BP (or 10 mmHg in diastolic BP) is associated with > two fold difference in death from several vascular causes. High BP in midlife is associated with lower cognitive function in later life. Among the components of the Metabolic Syndrome, high-BP and impaired fasting glucose are significant predictors of greater CV-morbidity and mortality. There is a lack of evidence on the age-related changes in most cardiovascular biomarkers but, using data from eight UK cohorts, a recent study evaluated the life course trajectories in BP and confirmed age-related changes in BP, independent of BMI.

Systolic increased from childhood, with a markedly midlife acceleration beginning at 40 years of age, and deceleration and reversion of these increases in late adulthood.

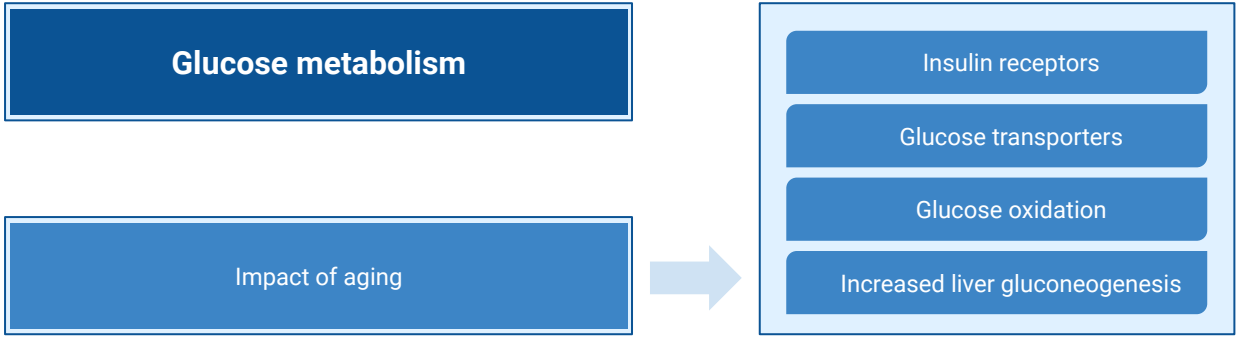
Lung function. From age 25, lung function assessed through forced expiratory volume (FEV1; the most common measure documented in epidemiologic studies) declines at approximately 32ml/year in men and 25 ml/year in women. Numerous population studies have documented an inverse association between FEV1 and aging-related endpoints including future total and cardiovascular mortality, cognitive function and fractures.

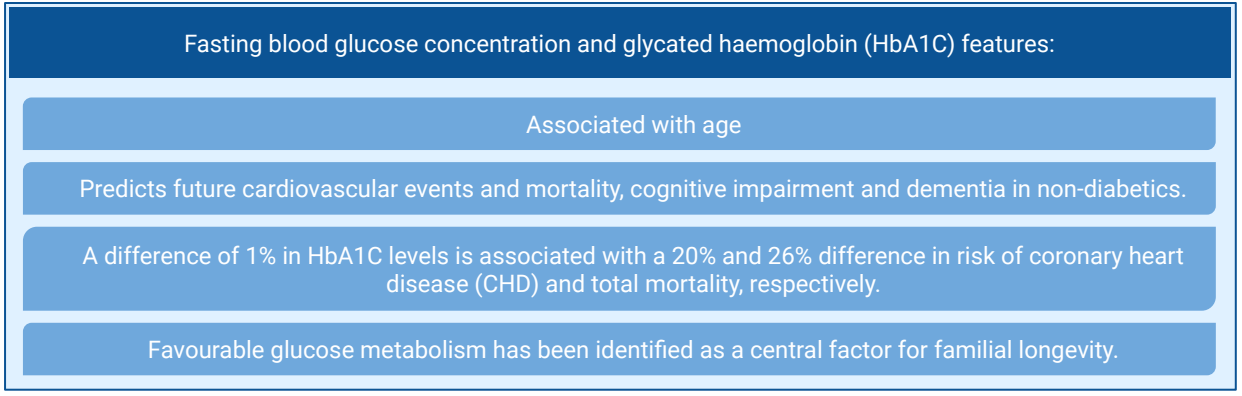
Bone health. Bone mass declines with age in both men and women although whether the decline is greater in women is debated. Techniques for measuring bone mass include dual x-ray absorptiometry (DXA), broadband ultrasound attenuation (BUA), and quantitative computed tomography (CT) and both site specific (hip or spine) DXA and heel BUA have been used extensively in epidemiologic studies. DXA is the most widely used method to assess bone mineral density and is the method of choice to diagnose osteoporosis. Bone mass or density (measured using DXA or BUA) predicts future fracture risk as well as mortality and other age-relevant health outcomes. BUA is an attractive alternative to DXA given its portability, lower cost, and no exposure to ionising radiation. A recent meta-analysis showed that BUA predicted fracture risk similarly to DXA.

Biomarkers of Physiology Domain Overview

Glucose metabolism. Aging is associated with alterations in several aspects of glucose metabolism, including insulin receptors and glucose transporters, leading to decreased glucose oxidation and increased liver gluconeogenesis

Biomarkers of dysregulated glucose metabolism including fasting blood glucose concentration and glycated haemoglobin (HbA1C) (an indicator of long-term average blood glucose concentration), are associated with age and predict future cardiovascular events and mortality, cognitive impairment and dementia in non-diabetics. A difference of 1% in HbA1C levels is associated with a 20% and 26% difference in risk of coronary heart disease (CHD) and total mortality, respectively. Favourable glucose metabolism has been identified as a central factor for familial longevity.

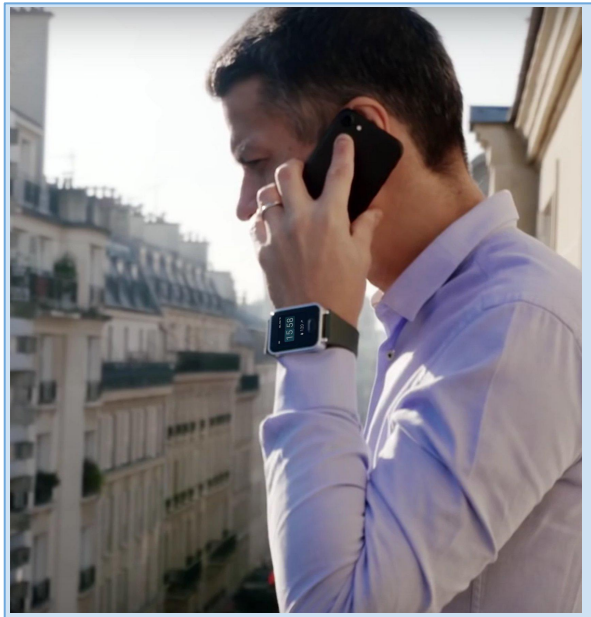




Weaknesses in the Physiology Biomarker Domain

Emerging biomarkers, for example fibrinogen, plasma cystatin C and brain natriuretic peptide, have been associated with increased risk of CV events and mortality, but it is uncertain if these offer advantages over well-established biomarkers. More research is needed on whether monitoring biomarkers over longer time periods, for example glucose concentration and ambulatory BP over 24 hours, or in response to a challenge, improves their predictive value.

The long-established age-related physiological biomarkers are usually measured at single points in time and it has been suggested that monitoring some of these biomarkers over longer time periods, e.g. glucose concentration and ambulatory blood pressure over 24h, may improve their predictive value but this needs to be tested in appropriate prospective cohort studies. The lack of evidence on the age-related changes of biomarkers could be addressed by mathematical modelling of longitudinal data.



From Continuous Glucose Monitoring (CGM) to cutting-edge insulin pumps, diabetes technology has come a long way. Health devices are becoming progressively less to non-invasive, and offer more options so that you can find what works best for you. CGM is an advanced way to check glucose readings in real-time or monitor glucose readings over indefinite periods of time. The CGM system works through a sensor placed in contact with your skin. It transmits readings to a recording device that could sounds an alarm if your blood sugar gets too high or low.

Sources Images: PKvitality.

Blood-based Biomarkers

Blood-based Biomarkers Overview

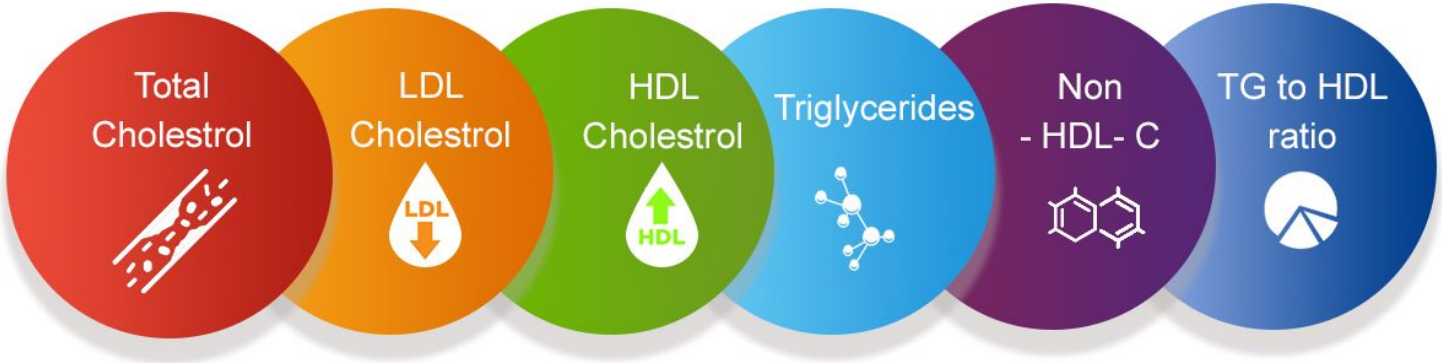
Most aging biomarkers measured within blood samples are related to cardiovascular function, glucose metabolism, inflammation, nutritional status, endocrinology and simply hematology. As already said, although there are many less well understood inflammation- and hemostasis-related biomarkers of cardiovascular function, the classical, widely measured, and well-documented physiological markers of risk of cardiovascular-related diseases remain some of the strongest biomarkers of aging: systematic reviews and meta-analyses provide strong evidence that the lipid profile is a predictor of morbidity and mortality; but there is a wide margin of error. Approximately 50% of the negatives for cholesterolemia and coronary heart disease risk through a conventional lipid profile are false negatives; implementing timely access to advanced lipid testing for the population would result in the effective prevention of at least a quarter of the prevalence of cardiovascular diseases, quite possibly much more.

Amongst the best studied aspects of immunosenescence is the age-related increase in inflammatory peptide biomarkers (Interleukins 6, 1β, Tumor Necrosis Factor-α and C-Reactive Protein), collectively termed *inflammaging*. Higher plasma concentrations of inflammatory factors such as IL-6 and TNF-α have been associated with lower grip strength and gait speed in older adults, demonstrating the interconnection between immune and functional status. CRP has been related to all-cause and specific causes of mortality and IL-6 was found to be a strong predictor of mortality.

Measurement of inflammatory markers has been conducted in centenarians. Centenarians demonstrate fewer signs of inflammaging. Whilst inflammatory peptides are either absent or lowered than that evident in younger cohorts, there is a corresponding increase in the levels of anti-inflammatory cytokines, such as IL-10. Importantly, much yet is to be understood with respect to the interactions between cytokines, the immune system and target organs. It is apparent that these inflammatory markers have many non-classical functions, including the modulation of metabolic functions, well beyond the classically described impact on inflammatory function.

Aging is associated with alterations in many aspects of metabolic and hormonal function, including altered expression of cellular insulin receptors and glucose transporter units in target tissues. Within these tissues there is corresponding changes in carbohydrate metabolism including decreased cellular glucose oxidation. These alterations result in a lowered glucose tolerance as measured by impaired ability to lower blood glucose after a standard glucose load. There are several measures of glucose tolerance with the clinically accepted measures for diagnosis of diabetes mellitus being the fasting and postprandial blood glucose concentration. Glycated hemoglobin, a measure of usual glucose concentrations over the preceding few months, which does not require fasting or a glucose challenge, has also been suggested as a feasible indicator of glucose metabolism.

Main Predictors of Morbidity in the Lipid Profile



The **Standard Lipid Profile** (image) test is used as part of a cardiac risk assessment to help identify an individual's risk of heart disease and to help make decisions about suitable treatment if there is a borderline or high risk. The results of a standard lipid profile test are considered along with other risk factors of heart disease such as lifestyle, family health history of a heart attack before the age of 50, family history of elevated cholesterol level, obesity, etc., to develop a plan of treatment and follow-up.

However, there are serious limitations to relying solely on the standard cholesterol panel. The well-known Framingham Study illustrated that the higher the cholesterol, the higher the statistical risk of a heart attack; nonetheless, a frightening number of heart attacks still occur every day in people whose cholesterol values are seemingly normal. In fact, the American Heart Association reports that 50% of men and 64% of women who died suddenly of coronary heart disease had no previous symptoms. Scientists, on the other hand, have developed more advanced blood tests that can far more accurately gauge risks of heart disease. An **Advanced Lipid Test** augments the standard cholesterol profile with additional measurements that can identify several risks related to cardiovascular disease. These tests not only offers a comprehensive assessment of cardiovascular risk, but also supplies vital information that can help patients and clinicians formulate a customized disease-prevention program and measure its progress over time. This powerful diagnostic tool can help take the steps necessary to avoid preventable health catastrophes — like heart attack and stroke— today. An Advanced Lipid Test is performed just like a traditional cholesterol panel: a technician or nurse draws blood and submits it to a laboratory. At reasonable cost, the test provides a lot more data than routine cholesterol tests and expands on this information. The comprehensive information derived from an advanced test enables physicians to more accurately predict their patients' risk of heart disease, and to customize more aggressive, patient-specific treatment plans.

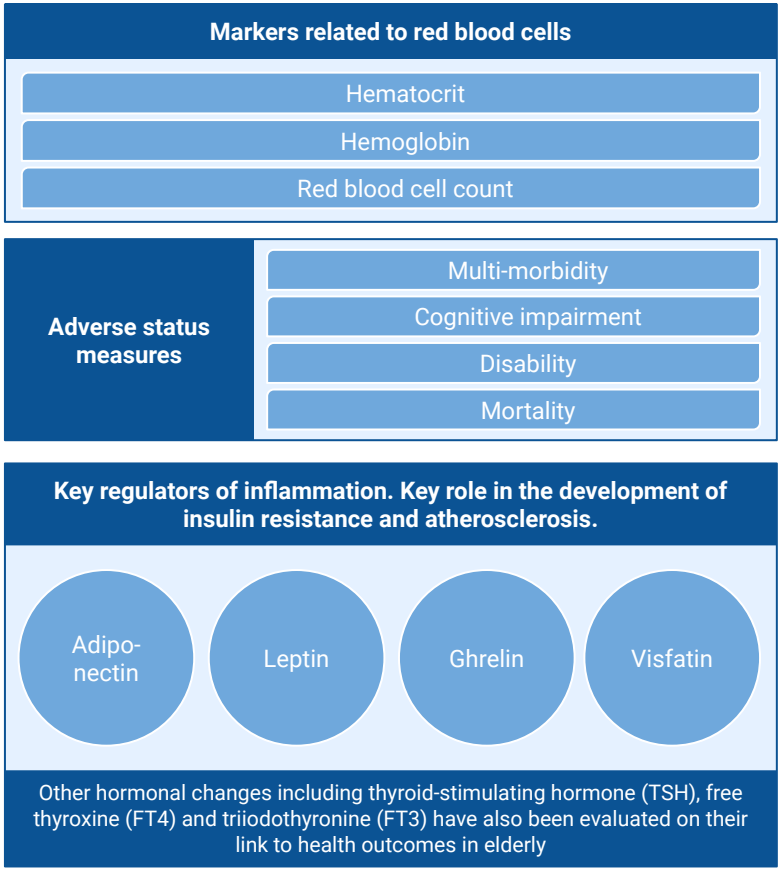
Sources Life Extension.

Blood-based Biomarkers Overview

Recently it was shown that markers related to red blood cells, more specifically hematocrit, hemoglobin and the red blood cell count are associated with significantly higher chances of adverse health-status measures such as multi-morbidity, cognitive impairment, disability and mortality. Age-related changes in the endocrine system are very well established including a decline in the sex hormones testosterone and estrogens due to andropause and menopause, and the reduced production of Growth Hormone and Insulin-Like Growth Factor-1 (Somatopause).

The more recently discovered adipokines such as adiponectin, ghrelin, leptin and visfatin are key regulators of inflammation, insulin resistance as well as of central functions such as appetite regulation. Alterations in serum adipokine levels have been linked with an increased risk of obesity and metabolic syndrome. Interestingly, the concentration of adiponectin appears to change with age and is linked with age-related health outcomes, however further research on the association between aging and adipokines is required.

Other hormonal changes including thyroid-stimulating hormone (TSH), free thyroxine (FT4) and triiodothyronine (FT3) have also been evaluated on their link to health outcomes in elderly, but only low FT3 levels were associated with an increased risk for morbidity and mortality. These findings are consistent with other studies investigating aged populations, showing an association of low serum FT3 with reduced parameters of physical performance and muscle strength, as well as an increased disease-burden and mortality.

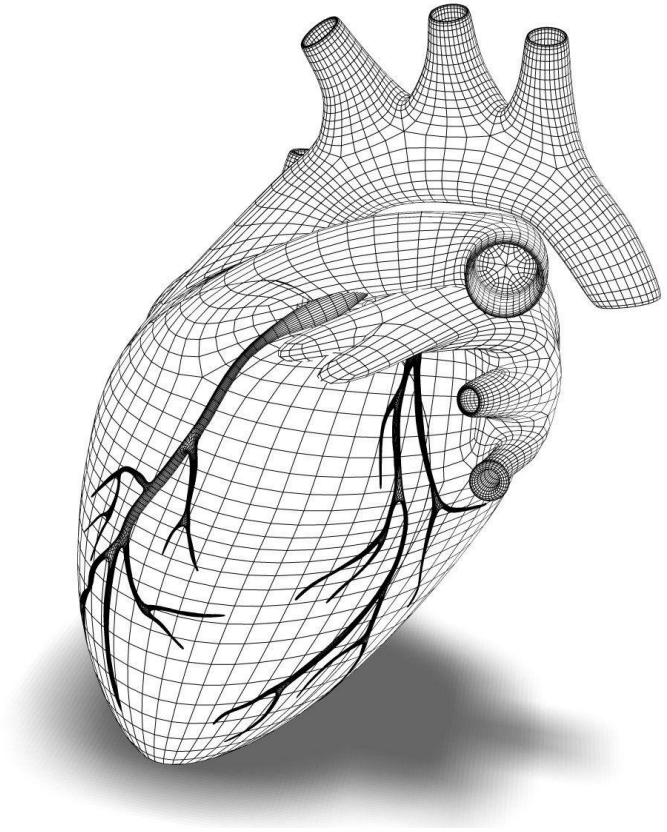


Blood-based Biomarkers Overview

Nutrition-related parameters are diverse, although studies have tended to focus primarily on a small subset of micronutrients including the vitamins D, B12, B6 and folic acid. However, data are not convincing, with limited evidence that suppressed vitamin D levels are associated with increased overall morbidity and cognitive impairment.

Other very interesting aging markers are N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponin, both of which are highly linked to myocardial damage. Recently it has been shown that NT-proBNP, which is elevated in the presence of heart failure, is associated with multi-morbidity, cognitive impairment and mortality, which makes NT-proBNP an informative general marker of age-related myocardial dysfunction. Cardiac troponin is associated with physiological renewal or remodeling of the myocardium. It is significantly correlated to NT-proBNP . Despite their validity as predictors for cardiac damage and cardiovascular diseases, both markers increase with age, importantly until very old age, in both male and female healthy subjects, which successfully qualifies them as biomarkers for human aging.

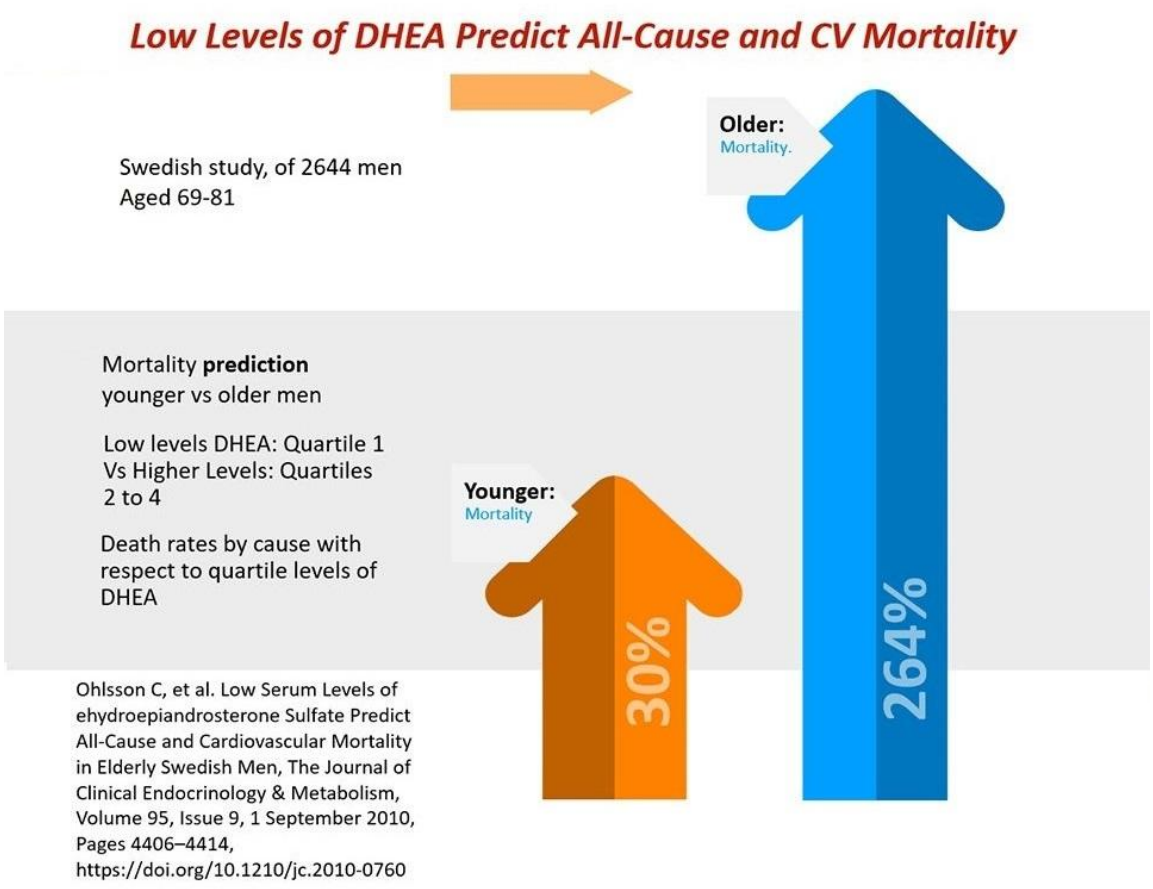
Despite the apparent relevance of many of these blood-borne measures, longitudinal data to precisely identify the predictive value of these markers prior to the onset of ill health are scarce. There is, however, substantial evidence that the timely analysis of blood borne biomarkers should be a common feature of geriatric care, with the need to establish normative standards and appropriate age-related reference ranges.



Biomarkers of Endocrine Function

Age-related changes in the endocrine system, particularly the sex hormones, are well recognised and have established causal links with health outcomes. This area includes on sex hormones, the HPA axis, growth hormone, IGF-1, melatonin, adipokines and thyroid hormones, etc

The strongest evidence supporting relationships with aging emerged for testosterone, estrogen, DHEAS, and GH/IGF-1. For each of these markers there was strong consensual evidence from longitudinal studies that changes were linked with risk of premature mortality and/or physical frailty. For some endocrine biomarkers, the relationship with aging appears to be non-linear. For example, the limited available evidence has shown that both high and low IGF-1 is related to mortality risk. Whilst DHEAS declines with aging, it is worth noting that a few studies reported no association with mortality; however, low serum DHEAS is almost always associated with increased mortality and, in the aforementioned few studies, generally associated with increased mortality in older women with concurrent frailty and also with frailty in men.

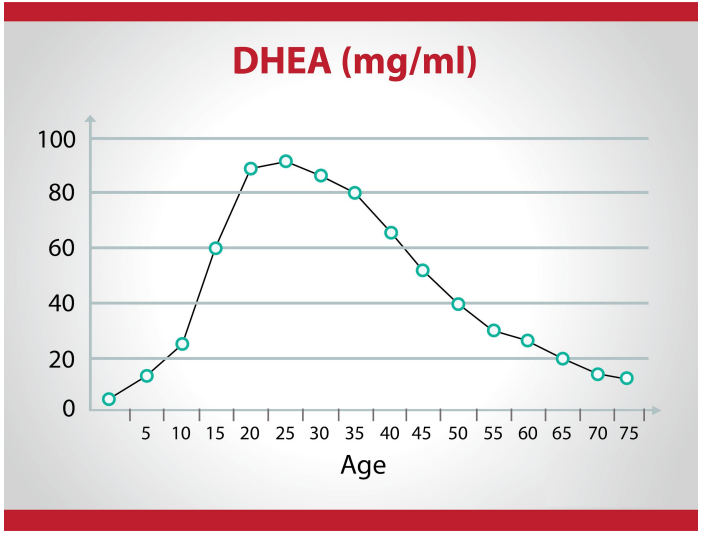


Biomarkers of Endocrine Function

Hormone replacement studies add to the evidence for a causal link to age-related physical and psychosocial decline. In this respect, the strongest associations are for both testosterone and estrogen and risk of physical frailty and bone health. There is evidence that circulating concentrations of melatonin and of adiponectin decline with age but these relationships have been investigated in only a few longitudinal studies. Adiponectin shows the strongest association with mortality even after controlling for BMI or change in BMI. Cortisol, a stress hormone produced in the adrenal cortex and a component of the HPA axis, has been associated with age-related disease and disability. There is evidence from longitudinal studies that abnormal cortisol secretion patterns are associated with increased BP, impaired glucose metabolism (fasting insulin and insulin/glucose ratio), and increased incidence of CVD and type 2 diabetes in men. Recently, associations between heightened cortisol reactivity to stress and coronary artery calcification have been identified which may influence the risk of coronary heart disease and hypertension.

Strong consensual evidence from longitudinal studies indicates that testosterone, estrogen, DHEAS growth hormone and IGF-1 are linked with risk of premature mortality and physical frailty. For some biomarkers, the relationship with aging appears to be non-linear, for example both high and low IGF-1 are related to greater mortality rates. DHEAS declines with age from the third decade onwards and low DHEAS is associated with increased mortality in older subjects with concurrent frailty. Hormone replacement studies suggest causal links for both testosterone and estrogen and risk of physical frailty, bone and muscle health. Cortisol is associated with age-related disease and disability, and abnormal cortisol secretion patterns with increased blood pressure, impaired glucose metabolism, insulin resistance and increased incidence of CVD and type 2 diabetes in men. The Cortisol:DHEAS ratio is even more precise in this regard.

Regarding the **weaknesses of endocrine biomarker**, longitudinal evidence is needed to enhance understanding of the relationships between cortisol, DHEAS, cortisol:DHEAS ratio, adipokines (adiponectin, leptin, ghrelin), somatostatin, and ageing, frailty and mortality.



Biomarkers of Endocrine Function

For these reasons, we conducted what may be the first human clinical trial designed to reverse aspects of human aging, the TRIIM (Thymus Regeneration, Immunorestoration, and Insulin Mitigation) trial, in 2015–2017. The purpose of the TRIIM trial was to investigate the possibility of using recombinant human growth hormone (rhGH) to prevent or reverse signs of immunosenescence in a population of 51- to 65-year-old putatively healthy men, which represents the age range that just precedes the collapse of the TCR repertoire. rhGH was used based on prior evidence that growth hormone (GH) has thymotrophic and immune reconstituting effects in animals and human HIV patients. Because GH-induced hyperinsulinemia is undesirable and might affect thymic regeneration and immunological reconstitution, we combined rhGH with both dehydroepiandrosterone (DHEA) and metformin in an attempt to limit the “diabetogenic” effect of GH. DHEA has many effects, in both men and women, that oppose deleterious effects of normal aging. Metformin is a powerful calorie restriction mimetic in aging mice and has been proposed as a candidate for slowing aging in humans. Neither DHEA nor metformin are known to have any thymotrophic effects of their own.

Obvious qualitative improvements in thymic MRI density were observed. Quantitatively, the overall increase in the thymic fat-free fraction (TFFF) was significant, implying a restoration of thymic functional mass. Bone marrow, similar to thymus, showed a pattern of increased BMFFF with increased baseline fat content. This difference plus the more robust replacement of thymic vs. bone marrow fat is consistent both with a specific reversal of thymic involution and with possible stimulation of bone marrow T-cell progenitor production by GH. Trial volunteer epigenetic ages were lower than their chronological ages at baseline, and epigenetic age was significantly decreased by treatment based on the results of all four epigenetic clocks, with a mean reversion after 12 months of about 2.5 years in each subject.

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Reversal of epigenetic aging and immunosenescent trends in humans

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Abstract

Epigenetic “clocks” can now surpass chronological age in accuracy for estimating biological age. Here, we use four such age estimators to show that epigenetic aging can be reversed in humans. Using a protocol intended to regenerate the thymus, we observed protective immunological changes, improved risk indices for many age-related diseases, and a mean epigenetic age approximately 1.5 years less than baseline after 1 year of treatment (−2.5-year change compared to no treatment at the end of the study). The rate of epigenetic aging reversal relative to chronological age accelerated from −1.6 year/year from 0–9 month to −6.5 year/year from 9–12 month. The GrimAge predictor of human morbidity and mortality showed a 2-year decrease in epigenetic vs. chronological age that persisted six months after discontinuing treatment. This is to our knowledge the first report of an increase, based on an epigenetic age estimator, in predicted human lifespan by means of a currently accessible aging intervention.

1 INTRODUCTION

Population aging is an increasingly important problem in developed countries, bringing with

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Metrics

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Details

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lymphocyte-to-monocyte ratio
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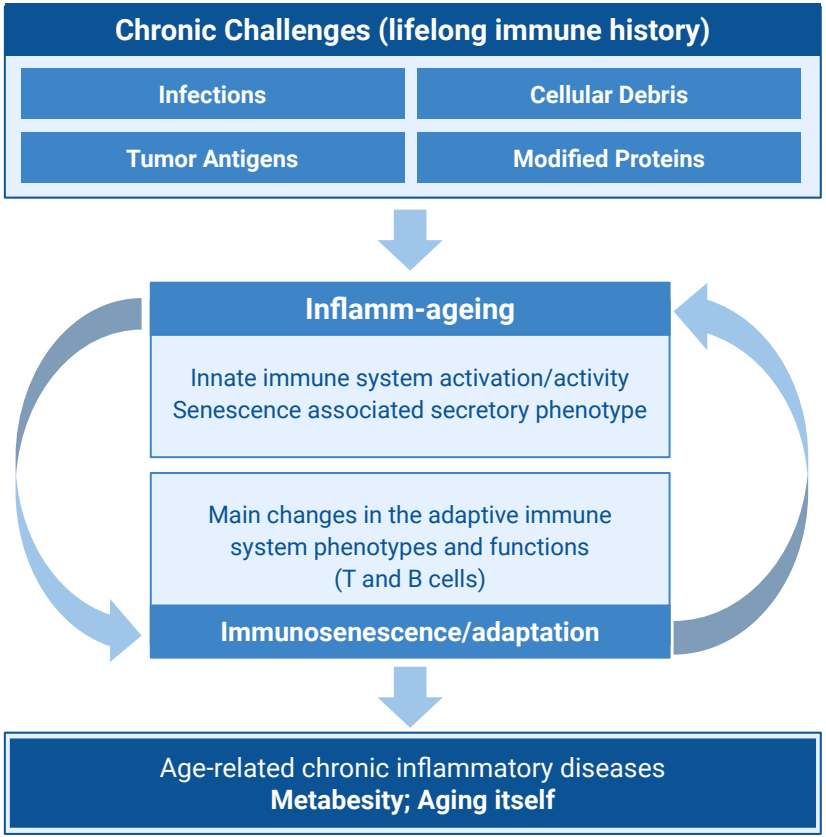
PD-1
PSA
thymic regeneration

Sources Steve Horvath, et al. Reversal of epigenetic aging and immunosenescent trends in humans. *2019.*

Biomarkers of Immune Function Overview

Whilst the field of immunology is well developed, the study of age-related decline in immunity, termed **immunosenescence**, is more recent. Here we focused on age-related immune function and inflammatory factors. Longitudinal studies comparing immune cells or function with mortality, or with age-related functions such as infection rates or vaccination responses, are scarce.

Two octogenarian and nonagenarian studies assessing immune markers (T-cell phenotype, cytomegalovirus serostatus and pro-inflammatory cytokine status) with subsequent mortality have been the basis for the development of the Immune Risk Profile (IRP; defined by an inverted CD4/CD8 ratio and associated with increased numbers of CD8 + CD28 cells), which is associated with mortality in those over 60 years. A limitation of the IRP is its narrow scope since it does not consider innate immune factors such as natural killer cell (NK Cell) function, which is linked with infection rates and mortality. The best studied aspect of immunosenescence is the age-related increase in systemic inflammatory cytokines, termed **inflammageing**. Higher plasma concentrations of IL-6 and TNF-α are associated with lower grip strength and gait speed in older adults. Centenarians show fewer signs of aging of the immune system although some inflammageing is seen.



Sources Image data: Tamàs Fulop, et al. From Inflamm-Aging to Immunosenescence. *2019.*

Biomarkers of Immune Function Weaknesses

Longitudinal studies should examine relationships between number and function of T cells, neutrophils, NK cells, B cells, and mortality, risk of age-related disease and wellbeing in later life. Given the switch from lymphoid to myeloid cell production with age, the *lymphocyte/granulocyte ratio* is a potentially useful biomarker of healthy aging. The Immune Risk Profile needs validation in younger people and should be expanded to include measures of immune function such as infection incidence or vaccination response.

Telomere length in leukocytes, including lymphocytes and monocytes, has received much attention. Despite its association with aging in several cohort studies, it is likely that shortened telomeres are also a marker of infection frequency so that leukocyte telomere length may not be a reliable index of biological aging. Lymphocytes proliferate rapidly in response to their cognate antigen and unlike most somatic cells have the ability to extend their telomeres by inducing telomerase expression but, eventually, this is insufficient to prevent lymphocyte telomere length shortening with age. Further studies of telomere length and aging should include investigation of exposure to infections and CMV seropositivity as possible confounders. In the Newcastle 85+ Study and other studies thus far leukocytes' telomere length was uninformative about health status.

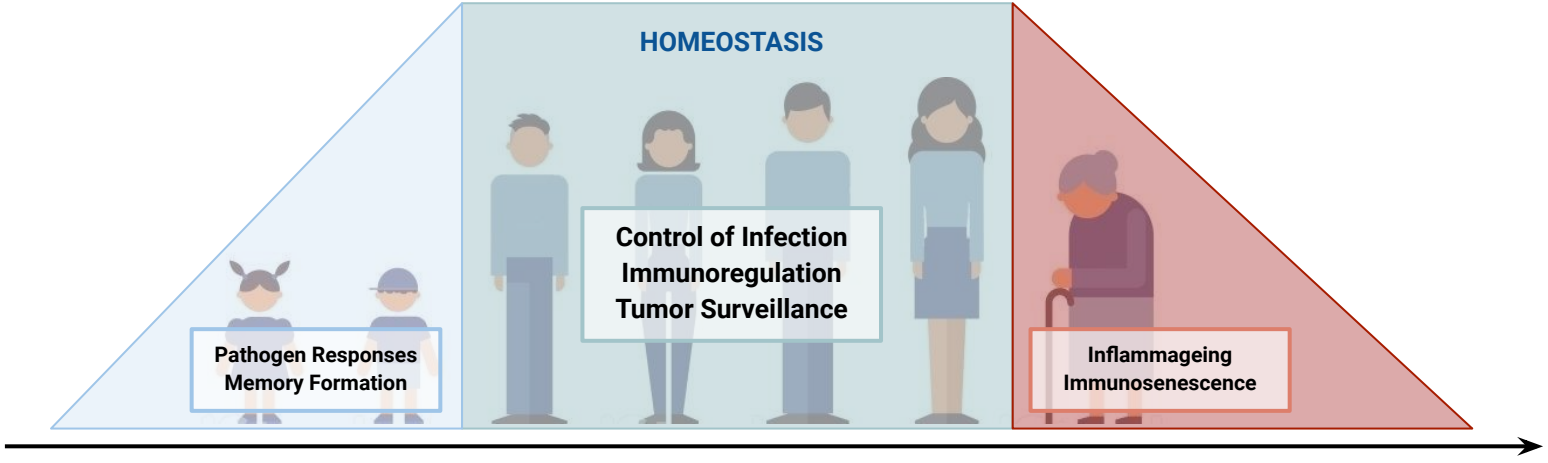
The immune system protects the organism from pathogens and also from damaged or altered tissues, cells (as occurs with cancer or traumatic injury) and molecules (as happens in phenomena such as loss of proteostasis, characterized by the loss of structural integrity of proteins, particularly long-lived proteins or LLP), whilst not damaging the organism's own tissues. In humans, the immune system develops a memory of exposure to a pathogen or particular environmental molecules, so that when those threats are encountered a second time the response is rapid and specific to that agents. This so-called **adaptive immune system**, based on lymphocytes activity, is also the basis of the vaccination response.

It is clear that each of these aspects of immune function declines with age; e.g. susceptibility to both bacterial and viral pathogens increases with age, the incidence of cancer is age-related as is loss of tolerance to one's own tissues, evidenced by increased autoimmunity. In addition, the ability to mount an adequate, protective vaccination response also deteriorates with age. This age-related decline in immunity is termed immunosenescence and, whilst the field of immunology is well developed, the study of immunosenescence is more recent, with papers beginning to appear in the 1980's.

Biomarkers of Immune Function Weaknesses

The best studied aspect of immunosenescence is the age-related increase in inflammatory cytokines (IL6, IL1β, TNFα and CRP) which is termed inflammageing. Higher plasma concentrations of inflammatory factors such as IL-6 and TNF-α have been associated with lower grip strength and gait speed in older adults. Measurement of inflammatory cytokines has been incorporated into longitudinal studies and have also been studied in centenarians. The latter group shows fewer signs of aging of the immune system, including the Immune Risk Profile, and inflammageing is absent or much reduced, being counteracted in part by high levels of anti-inflammatory cytokines such as IL-10.

Although there is no exact understanding about the causes of inflammaging and the key aspects of their feedback with immunosenescence, a common finding seems to involve a dysregulation of the cytokine network and its homeostasis. Several common molecular pathways have been identified that seem to be associated with both aging, low-grade inflammation and immunosenescence, but these relationships are not yet sufficiently clarified.



Molecular-Level Biomarkers Overview

Common theories of aging, where age linearly correlates with and/or is caused by the accumulation of reactive oxygen species (ROS), DNA damage, mitochondrial dysfunction, impaired antioxidant defense and shortening of the telomeres, are well established in humans. However it has been reported that many of these markers increase up to a certain age, most commonly coinciding with the statistical life-expectancy. Thereafter, a plateau or even a decrease in the level of some of these biomarkers has been described.

Supported by the free radical theory of aging, it is widely accepted that the production of ROS by mitochondria accumulates over the lifespan and leads to a state of chronic oxidative stress at old age. As antioxidant defense mechanisms and DNA repair capacity seem to be impaired in the elderly, or at least be overwhelmed by the damage occurrence rate, DNA damage has been proposed to be a consequence of aging. Impaired DNA stability and genome instability increase the frequency of cytogenetic aberrations, which in turn is highly linked to age-related diseases such as cancer, diabetes, cardiovascular diseases and cognitive decline. However, after linearly increasing until the age of 60–70 years, chromosomal damage tapers and the rate of damage diminished with increasing age (over 85 years). Notably, the same seems to be true for telomeres, the protective ends of the chromosomes. Longer telomeres and higher telomerase activity contribute to the stability of the genome, to DNA integrity and are positively correlated with the aging process. These are evidently adaptive-based processes that have been consolidated and deepened throughout the pathway of evolution by natural selection, cushioning the effects of aging on the human species.

Both, the “regular” aging process and the development of chronic diseases are accompanied by increased DNA damage, chromosomal damage, and telomere shortening. Importantly, people exceeding the statistical life-expectancy, and especially the very oldest age-groups including nonagenarians (90–99 years), centenarians (100–109 years) and super-centenarians (110 years and older), demonstrate a different picture of age-related diseases compared to study cohorts at or below life-expectancy. Furthermore, an increasing amount of data suggests that chromosomal stability, DNA repair activity, and antioxidant defense capacity in successfully aged subjects is comparable to younger cohorts.

Taken together, very old humans seem to contradict traditional theories of aging regarding the age-related accumulation of DNA damage, genome instability and telomere shortening by demonstrating better DNA repair capacity and higher telomerase activity, even comparable to much younger cohorts. Whether the superior resilience of “successful” agers originates from hereditary factors or an outstanding healthy lifestyle remains a field for future research. Conclusively, markers of DNA integrity, genome stability, antioxidant defense or telomere length based on current evidence do not meet the criteria for a valid biomarker for aging.

Molecular-Level Biomarkers Overview

Bilirubin, the principal tetrapyrrole, bile pigment and catabolite of haem, is an emerging biomarker to monitor resistance against chronic non-communicable diseases. Mildly elevated serum bilirubin levels have been reported to be strongly associated with reduced CVD-related mortality and associated risk factors. Recent data also link bilirubin to all-cause mortality and to other chronic diseases, including cancer and type 2 diabetes mellitus. Therefore, there is evidence to suggest bilirubin as a biomarker for reduced chronic disease prevalence and for the prediction of all-cause mortality, but also as a novel biomarker for successful aging.

Advanced Glycation End-products (AGEs) represent further biomarkers with incredible potential to monitor healthy aging. Protein modifications such as the non-enzymatic protein glycation are common posttranslational modification of proteins resulting from reactions between glucose and the amino groups of proteins. This process, better known as “Maillard reaction”, leads to the formation and accumulation of AGEs throughout life. Interestingly, the AGEs of long-lived proteins (LLPs) such as collagens and cartilage accumulate during normal aging; these are proteins that barely experience or do not experience replacement throughout life, some with a half-life of more than 100 years. AGEs are involved either directly or through interactions with AGE-receptors in the pathophysiology of numerous age-related diseases including cardiovascular diseases, amyloidosis, neurodegeneration, diabetes and renal disease, among multiple others.

Metallothioneins (MTs) are low molecular weight, cysteine rich, zinc-binding proteins, which are down-regulated in older age groups. MTs exert an essential role in zinc-mediated transcriptional regulation of genes involved in growth, proliferation, differentiation, and development, pathways of importance in neural function. There is experimental evidence that MTs are induced in the aging brain as a defensive mechanism to attenuate oxidative and nitrative stress. MTs may also act as free radical scavengers by inhibiting Charnoly body formation, thus contributing to protecting mitochondrial function as a mechanism of neuroprotection in the aging brain.

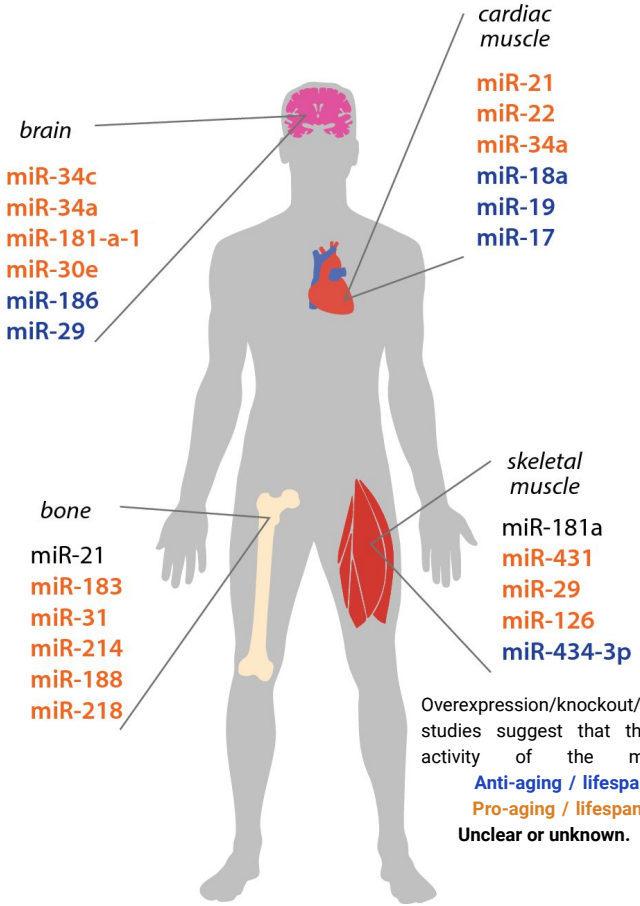
Very recently the interesting model of the *epigenetic clock* has been advanced with the analysis of peripheral blood mononuclear cells isolated from semi-supercentenarians and their offspring. The epigenetic clock is a multivariate estimator of chronological age based on DNA methylation levels of 353 dinucleotide markers known as Cytosine phosphate Guanines (CpGs). These cytosines experience methylation selectively throughout life, they are hot spots of greater probability and incidence of methylation. Extent and patterns of CpGs are independently associated with chronological age and mortality; further data is required to understand whether these changes are causal or a consequence of aging, but it is almost unquestionable that the first is true.

Molecular-Level Biomarkers Overview

Epigenetic changes are but one of a number of emerging molecular biomarkers of altered molecular function in aging that may be predictive of health status. Recent studies have examined the novel molecular marker p16INK4a, which is classically known for its capacity to inhibit cyclin-dependent kinase activity. Long-term p16INK4a expression is a promoter of cellular senescence, a process of irreversible cell-cycle arrest and the loss of regenerative capacity. Therefore, precise regulation of p16INK4a is essential to tissue homeostasis, maintaining a coordinated balance between tumor suppression and aging. As yet, studies in human populations and differing cell types have yet to be conducted to provide evidence of its potential as a biomarker of healthy aging.

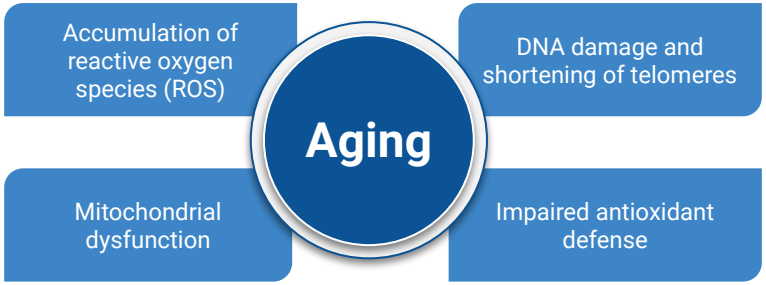
Finally, microRNAs (miRNAs), single-stranded and non-coding RNA molecules of 21–23 nucleotides that regulate a broad spectrum of biological activities, have been proposed as signatures of aging. These small RNA molecules were initially demonstrated to contribute to aging in the worm *Caenorhabditis elegans* and show differential expression levels in tissues of young and old animal models. Most interestingly miRNAs are stable molecules even in serum and/or plasma, hence are regarded as promising biomarkers in the clinical setting.

Studies also demonstrate a specificity of age-related health loss, with the ability to differentiate the onset of Alzheimer's disease and/or mild cognitive impairment from cognitively normal age-matched controls with some degree of accuracy utilizing a miRNA signature analysis. Furthermore, miRNAs might also serve as circulating biomarkers for cardiovascular aging or aging-associated diseases, but further research needs to be conducted to evaluate their sensitivity, selectivity and potential as predictive biomarkers for discriminating successful from non-successful aging.



Sources Image: Holly E. Kinser, et al. MicroRNAs as modulators of longevity and the aging process. *2019.*

Molecular-Level Biomarkers Overview



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Conclusively, markers of DNA integrity, genome stability, antioxidant defense or telomere length based on current evidence do not meet all the criteria for a valid biomarker for aging. **And epigenetic marks do**.

Bilirubin

Principal tetrapyrrole, bile pigment and catabolite of haem, is an emerging biomarker to monitor resistance against chronic non-communicable diseases.

Advanced glycation end products (AGEs)

Further biomarkers with some potential to monitor healthy aging. Protein modifications such as the non-enzymatic protein glycation are common posttranslational modification of proteins resulting from reactions between glucose and the amino groups of proteins.

Metallothioneins

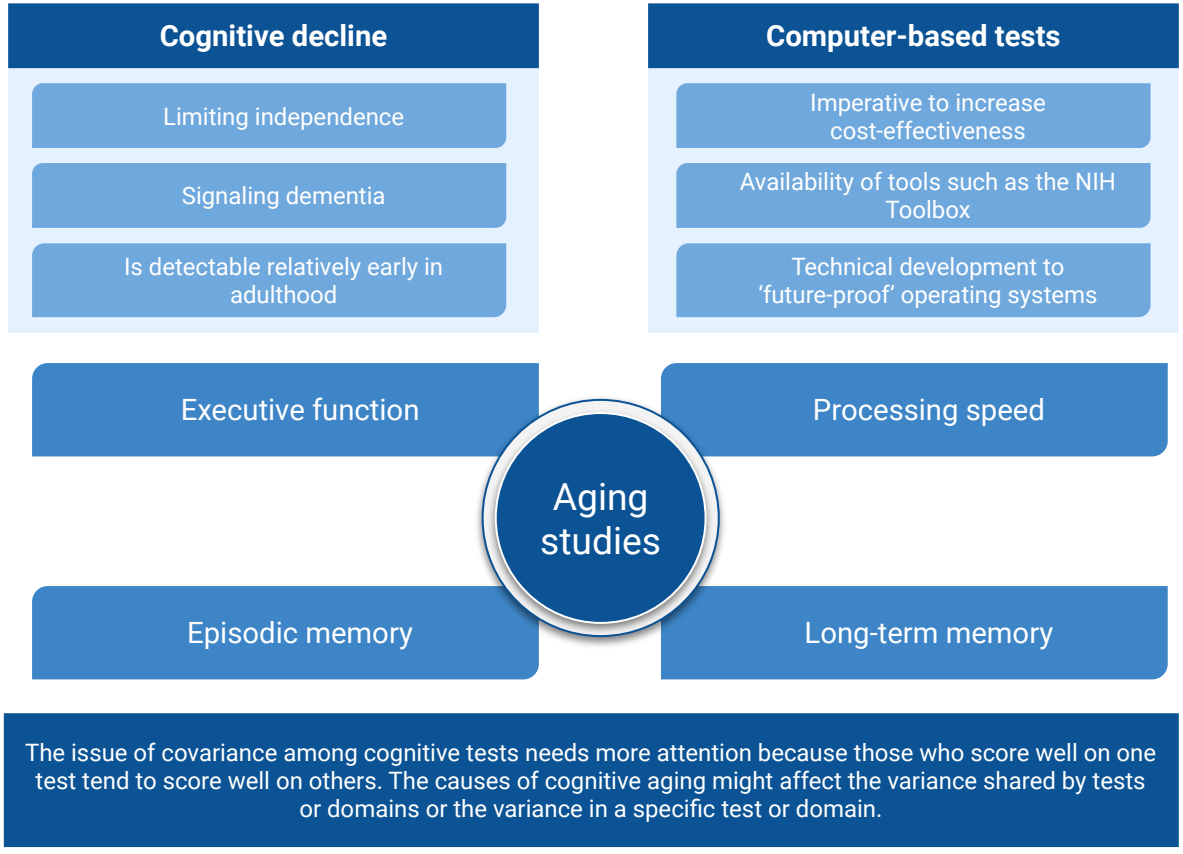
Low molecular weight, cysteine rich, zinc-binding proteins, which are down-regulated in older age groups

Cognitive Biomarkers

Cognitive Biomarkers Overview

Cognitive decline may limit independence and signal dementia, and, although debated, evidence indicates that the onset of cognitive decline is detectable relatively early in adulthood, for example from around 45 years of age or earlier in some functions.

Executive function, processing speed and episodic memory – are a possible minimum set of domains to be assessed in aging studies. If assessment time allows, tests of crystallised cognitive ability and non-verbal reasoning would be useful additions. Executive function is markedly affected by aging, exhibiting an inverted U-shape pattern across the lifespan. Processing speed declines progressively with age and is associated with greater mortality risk, cardiovascular and respiratory diseases. In addition, episodic memory is sensitive to brain aging and declines in individuals with mild cognitive impairment and neurodegenerative diseases. A standard deviation advantage in memory is associated with 21 % reduction in mortality risk among older individuals.



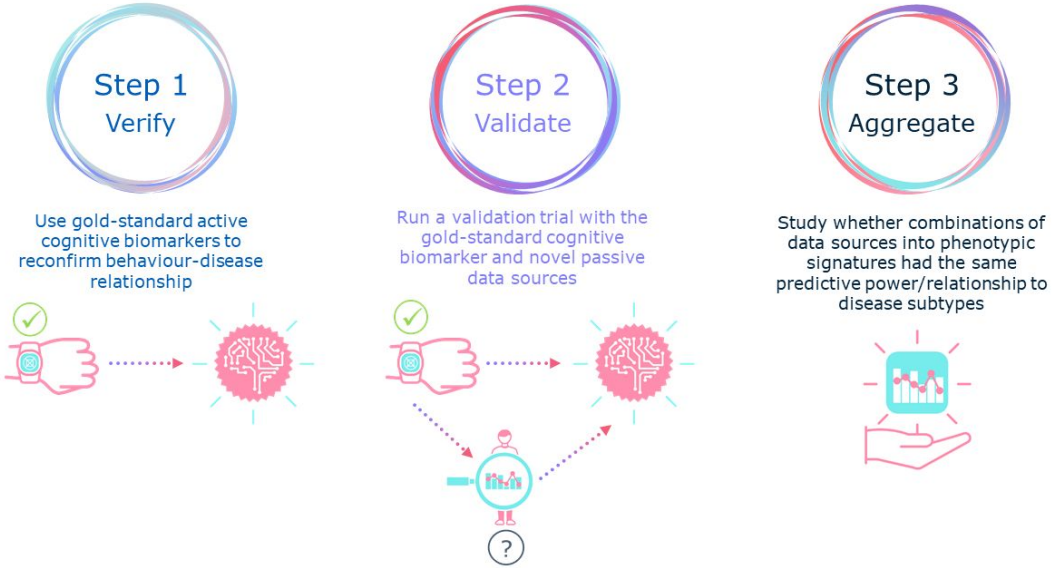
Cognitive Biomarkers Weaknesses

To date, computer-based tests are not widely used in major cohorts; availability of tools such as the NIH Toolbox and the imperative to increase cost-effectiveness are likely to drive the migration to digital methodologies. This will require that tests are supported by ongoing technical development to 'future-proof' operating systems and hardware. Where tests are administered repeatedly in the same individuals problems associated with practice and familiarity need to be addressed. The issue of covariance among cognitive tests needs more attention because those who score well on one test tend to score well on others. Timothy A. Salthouse and others have highlighted that the causes of cognitive aging might affect the variance shared by tests or domains or the variance in a specific test or domain.

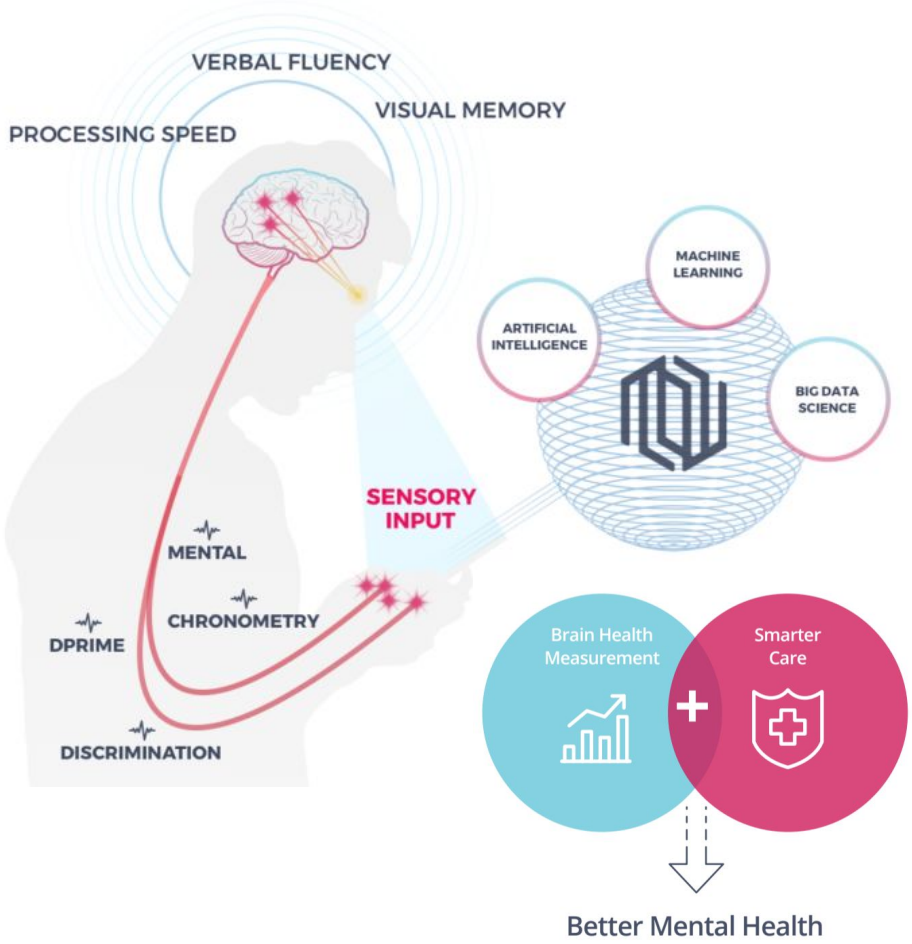
Passive biomarkers are a hot topic at the moment with the rise of digital phenotyping and the prospect of being able to monitor a person's health status non-invasively without the participant having to engage in specific tasks. To facilitate these passive biomarkers, large datasets are required with extensive validation in healthy and clinical populations.

Passive data sources can be combined to create complex phenotypic signatures or digital avatars which relate to a person's health or disease status. These can be enhanced by coupling passive data sources with active cognitive assessments to determine relationships with health.

Active cognitive biomarkers serve as both the immediate gold-standard endpoints for cognitive function, but also as the benchmark for training and validating novel passive measurements against.



Sources Cambridge Cognition | Jose Lara. *2015.*



Sources Images: [Mindstrong]

Panels of Biomarkers of Aging

Selected Biomarker Panels List

1. WellnessFX Premium, WELLNESSFX
2. Anti-Aging #4 Comprehensive Blood and Urine Test Panel, WALK-IN LAB
3. Aging Theranostic 1.0, OPEN LONGEVITY
4. InsideTracker Ultimate Plan, SEGTERRA
5. InsideTracker Inner Age, SEGTERRA
6. Biomarker Panel, UK BIOBANK
7. Healthy Aging Panel (Comprehensive), LIFE EXTENSION
8. Female/Male Saliva Profile II - Test Kit For 6 Hormone Level Imbalances, ZRT LABORATORY
9. 10 Hormone Saliva Test Kit, LABRIX
10. Adrenal Stress Profile, CELL SCIENCE SYSTEMS
11. Adrenal Check, FLUIDS iQ®
12. Comprehensive Adrenal Stress Profile, GENOVA DIAGNOSTICS
13. Oxidative Stress Analysis 2.0, GENOVA DIAGNOSTICS
14. Metabolic Analysis Profile (Organic Acids), GENOVA DIAGNOSTICS
15. Immune-Frame, RGCC
16. Cytokine Panel, MAYO CLINIC LABORATORIES
17. Salivary Cytokine Panel, SALIMETRICS
18. Advanced MethylDetox Profile, CELL SCIENCE SYSTEMS
19. Advanced MethylDetox Profile plus Telomere Length Test, CELL SCIENCE SYSTEMS
20. Genetic Age Test, CERASCREEN
21. AGE-Reader mu Test, DIAGNOPTICS
22. GlycanAge Test, GLYCANAGE
23. Viome Gut Intelligence™ Test, VIOME
24. SmartGUT™ Microbiome Test, SMARTDNA
25. Microba Insight™, MICROBA
26. Gut Microbiota Biohacker, TFTAK CENTER OF FOOD AND FERMENTATION TECHNOLOGIES
27. Health plus Ancestry Service, 23ANDME
28. Array Comparative Genomic Hybridisation (aCGH) RGCC, RGCC
29. ImmunoGenomic® Profile, GENOVA DIAGNOSTICS
30. NeuroGenomic™ Profile, GENOVA DIAGNOSTICS
31. CardioGenomicPlus™ Profile, GENOVA DIAGNOSTICS
32. PhysioAge Biomarkers of Aging Test, PHYSIOAGE
33. DiscoveryMAP v. 3.3 Panel, MYRIAD RBM
34. Explorer MAP™ v. 1.0, MYRIAD RBM
35. HumanMAP® v. 2.0, MYRIAD RBM
36. CardiovascularMAP® v. 3.0, MYRIAD RBM
37. InflammationMAP® v. 1.0, MYRIAD RBM
38. ImmunoMAP® v. 1.0, MYRIAD RBM
39. NeuroMAP™ v. 1.0, MYRIAD RBM
40. MetabolicMAP® v. 1.0, MYRIAD RBM
41. CytokineMAP A, MYRIAD RBM
42. CytokineMAP B, MYRIAD RBM
43. AngiogenesisMAP® v. 1.0, MYRIAD RBM
44. LEGENDScreen™ Human PE Kit, BIOLEGEND
45. LEGENDplex™ Human B Cell Panel (13-plex), BIOLEGEND
46. LEGENDplex™ Human CD8/NK Panel (13-plex), BIOLEGEND
47. LEGENDplex™ Human Th Cytokine Panel (13-plex), BIOLEGEND
48. Regulatory T-Cell Panel, ARUP LABORATORIES
49. Cytokine Panel, ARUP LABORATORIES
50. Cytokine Panel, TH1, ARUP LABORATORIES
51. Carnitine Panel, ARUP LABORATORIES
52. Hepatic Function Panel, ARUP LABORATORIES
53. B-Cell Memory and Naive Panel, ARUP LABORATORIES
54. Natural Killer Cell and Natural Killer T-Cell Panel, ARUP LABORATORIES
55. OMIP-004: In-Depth Characterization of Human T Regulatory Cells
56. OMIP-007: Phenotypic Analysis of Human Natural Killer Cells
57. OMIP-018: Chemokine Receptor Expression on Human T Helper Cells
58. OMIP-027: Functional Analysis of Human Natural Killer Cells
59. OMIP-029: Human NK-Cell Phenotypization
60. OMIP-039: Detection and analysis of human adaptive NKG2C+ natural killer cells

Selected Biomarker Panels List

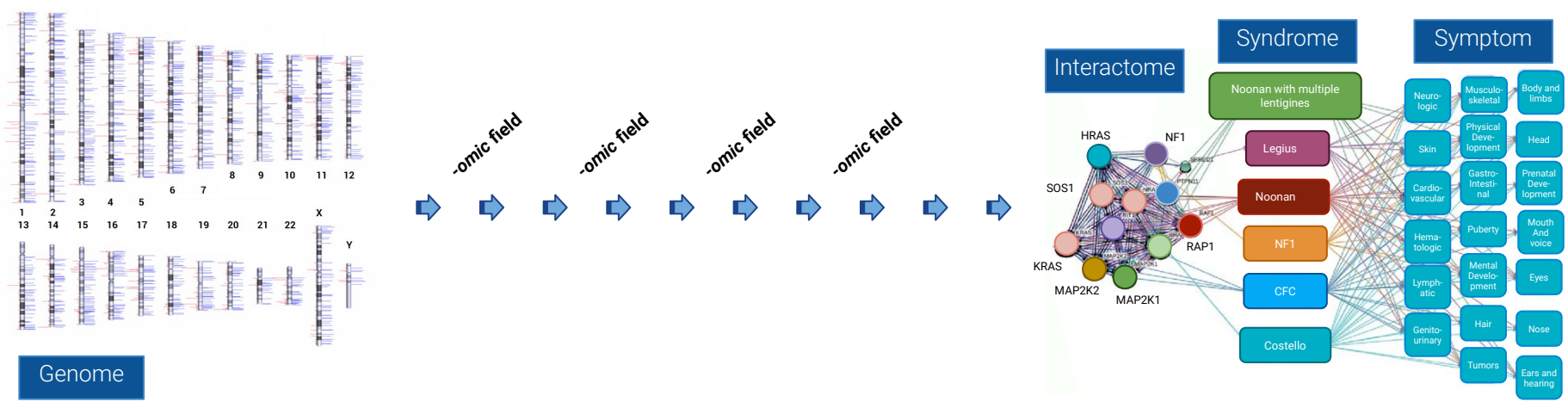
61. Cardiometabolic Panel, OLINK
62. Cell Regulation Panel, OLINK
63. Cardiovascular II Panel, OLINK
64. Cardiovascular III Panel, OLINK
65. Immune Response Panel, OLINK
66. Inflammation Panel, OLINK
67. Metabolism Panel, OLINK
68. Neurology Panel, OLINK
69. Neuro Exploratory Panel, OLINK
70. Oncology II Panel, OLINK
71. Oncology III Panel, OLINK
72. Organ Damage Panel, OLINK
73. Human v3 miRNA Assay, NANOSTRING
74. MiRXES ID3EAL miRNA Assay, MiRXES
75. OsteomiRTM - Validated Bone Biomarkers, TAmiRNA
76. ThrombomiRTM - Biomarkers of Platelet Function, TAmiRNA
77. ToxomiRTM - Biomarkers of Toxicity, TAmiRNA
78. DNAge™ Epigenetic Aging Clock, ZYMO RESEARCH
79. Epigenetic Age Analysis Version 2.0, OSIRIS GREEN
80. DNAge® Test, BIOVIVA
81. EpiHealth, CHRONOMICS
82. EpiAging, HKG EPITHERAPEUTICS
83. EpiSocialpsych, HKG EPITHERAPEUTICS
84. Targeted Sequencing For DNA Methylation Analysis, HKG EPITHERAPEUTICS
85. EpiLiver, HKG EPITHERAPEUTICS
86. EpiBreast, HKG EPITHERAPEUTICS
87. TeloYears plus Advanced Ancestry Tests, TELOYEARS
88. Telomere Length and Biological Age Testing, LIFE LENGTH
89. Telomere Length Test, CELL SCIENCE SYSTEMS
90. CD4+ T-Cell Recent Thymic Emigrants (RTEs), ARUP LABORATORIES
91. CD21 (Dendritic Cell) by Immunohistochemistry, ARUP LABORATORIES
92. CD57+ NK Cells, Peripheral Blood by Flow Cytometry, ARUP LABORATORIES
93. Phospho-H2AX (Ser139) Cellular Kit, CISBIO
94. Senescence Detection Kit, ABCAM
95. SPiDER-ßGal, DOJINDO MOLECULAR TECHNOLOGIES
96. Young.AI, INSILICO MEDICINE
97. Aging.AI, INSILICO MEDICINE
98. PhotoAgeClock, HAUT.AI
99. Haut.AI Skin Health, HAUT.AI
100. AgeMeter, CENTERS FOR AGE CONTROL
101. Health Reviser Platform, HEALTH REVISER
102. MEDIAGE™ Biological Age Measurement System, MEDIAGE
103. CarePredict Platform, CAREPREDICT
104. Enlitic Platform, ENLITIC
105. Freenome Platform, FREENOME
106. AI-Powered Radiology Assistant, ZEBRA MEDICAL VISION
107. PathAI Platform, PATHAI
108. Buoy Health Platform, BUOY HEALTH
109. BenevolentAI, BENEVOLENT
110. Tempus Platform, TEMPUS
111. KenSci Platform, KENSCI
112. Proscia Platform, PROSCIA
113. Google's DeepMind Health AI Platform, DEEPMIND TECHNOLOGIES
114. ICarbonX Platform, ICARBONX
115. Blood Chemistry Calculator, NOURISH BALANCE THRIVE
116. Ada - Symptom Checker App, ADA HEALTH GMBH
117. Babylon Health Platform, BABYLON HEALTH
118. Digital Nutrition Platform, ZIPONGO
119. Better Therapeutics Platform, BETTER THERAPEUTICS

Biomarker Panels

AGING ANALYTICS AGENCY

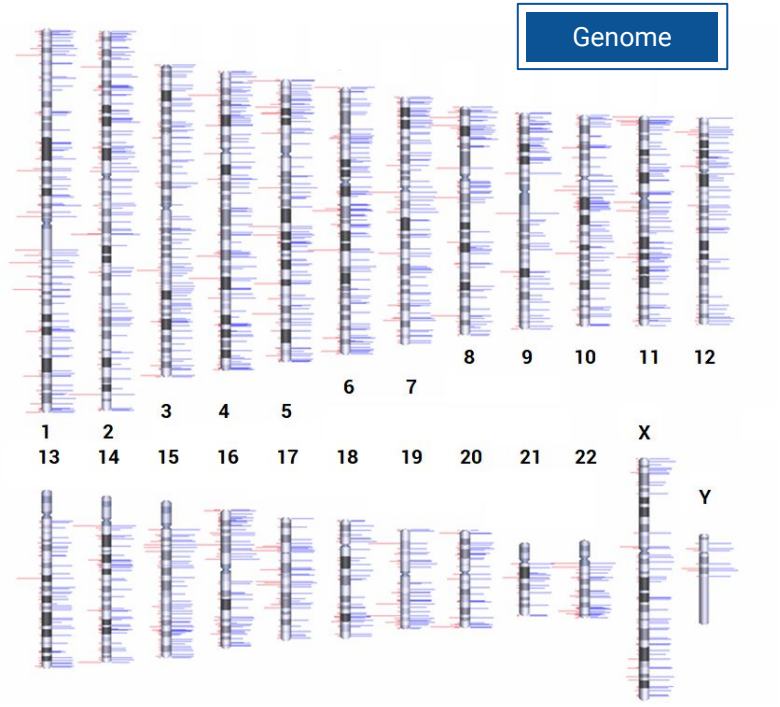
Given the heterogeneity and variability in any disease, a single biomarker may not be able to sufficiently reflect the pathological phenomenon itself or its underlying complexity. **Almost all single biomarkers have considerable fallibility.** This reason, coupled with the disruptive burst of biotechnology, the massive capture and aggregation of data and deep biomedical knowledge facilitated by frontier tech in the field of research and development, has kindled interest in and accelerate progress toward **Biomarker Panels** design.

A **Biomarker Panel** is a group of biomarkers that reflect different interconnected processes or parameters of a disease or health status, creating complex networks of biomedical outputs. In the particular context of aging biomarkers, a biomarker panel is some integrated composition of those biological indicators predicting functional capacity at a certain time in the future in more optimal ways than single biomarkers and chronological age itself.



Sources Image: T. Kunej, et al. RASopathies: Presentation at the Genome, Interactome, and Phenome Levels. *2016.*

Biomarker Panels



Genomics, metabolomics, proteomics, microbiomics and so forth, but fundamentally novel *multi-omics* approaches, are offering thumping amounts of biological data and ultra-modern insights on disease trajectories. These are all concise examples of **Comprehensive Panels of Biomarkers**.

These uses of numerous biomarkers assembled in Panels including *multi-omics* data and their deep analysis by AI platforms push back the boundaries of biomedical knowledge, health status characterization, diagnosis and early detection, and opens new doors for *Precision*, *Preventive*, *Personalized* and *Participatory* interventions; for P4 Medicine.

We aim to build an objective panel of biomarkers of the aging trajectory and healthy aging in humans, where healthy aging is defined as the maintenance of function for the maximal period of time. In a clear example of its usefulness, the inclusion of the same common biomarker panel of aging in diverse study designs and epidemiological surveys can enhance the value of those studies by allowing the standardization and validation of the surrogate endpoints, thus facilitating enhanced comparisons between studies and the pooling of data across studies.

The use of Biomarker Panels means more granular data, and more granular data translates into more finely tuned ways of performing risk and disease progression stratification for assignment to different care regimens and shift from late stage care to preventive medicine. This shift from treatment to prevention is ultimately leading to a coming age of Preventive Treatments and Precision Health, where patients are empowered with the tools necessary to become the drivers and engineers of their own health status; i.e., through the application of P4 Medicine in response to continuous monitoring of fluctuations in these aging biomarkers.

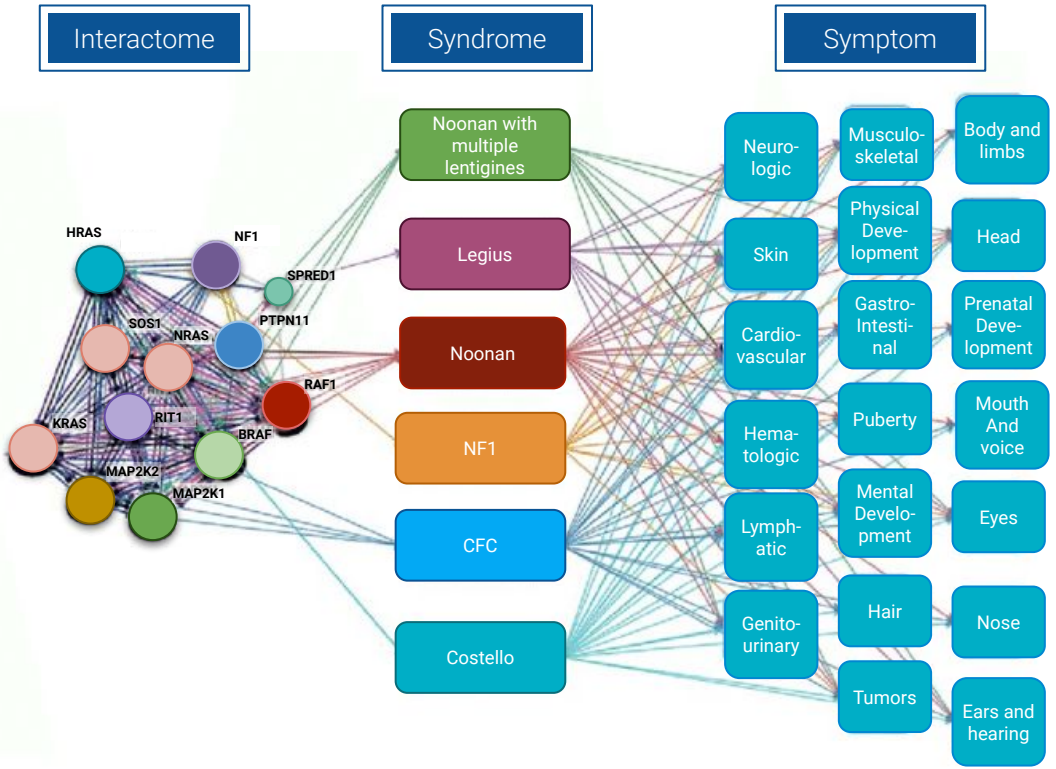
Biomarker Panels

AGING ANALYTICS AGENCY

Complex Biomarker Network.

It has previously been reported that gene/protein and phenotype networks could be assembled into an integrated network. The different units of all the *omic* levels are interconnected, weaving a complex network of biomarkers highly correlated with a disease, condition or biological trait or state: the Interactome. Thus, a pathology can be identified and corrected in multiple levels. More network data, greater predictive power and controllability of the biological state.

Clinical symptoms can be correlated with mutated proteins. According to T. Kunej et al., alignments between interactome and phenome levels can reveal new links between diseases, symptoms, *-omes* and knows genes, as well as connections between previously unrelated diseases, as in the illustration: a network model for 6 syndromes belonging to the RASopathy class of disorders; Noonan syndrome with multiple lentigines, Legius, Noonan, NF1, cardiofaciocutaneous and Costello syndromes, and the string associations between different levels of biomarkers for this set of disorders. This biomarkers network approach is rarely used in genomics, despite its potential for novel discoveries and medical interventions.



Sources Image: T. Kunej, et al. RASopathies: Presentation at the Genome, Interactome, and Phenome Levels. *2016.*

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
WellnessFX Premium	**WELLNESSFX**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Anti-Aging #4 Comprehensive Blood and Urine Test Panel	**WALK-IN LAB**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Aging Theranostic 1.0	**OPEN LONGEVITY**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
InsideTracker Ultimate Plan	**SEGTERRA**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
InsideTracker Inner Age	**SEGTERRA**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Biomarker Panel	**UK BIOBANK**	PANEL	Approved for Clinical Use	**Epidem. or Theoretical Panel Only** (BAI=0; ACTIONAB.=0)
Healthy Aging Panel (Comprehensive)	**LIFE EXTENSION**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Female/Male Saliva Profile II - Test Kit For 6 Hormone Level Imbalances	**ZRT LABORATORY**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
10 Hormone Saliva Test Kit	**LABRIX**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Adrenal Stress Profile	**CELL SCIENCE SYSTEMS**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
Adrenal Check	**FLUIDS iQ®**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Comprehensive Adrenal Stress Profile	**GENOVA DIAGNOSTICS**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Oxidative Stress Analysis 2.0	**GENOVA DIAGNOSTICS**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Metabolic Analysis Profile (Organic Acids)	**GENOVA DIAGNOSTICS**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Immune-Frame	**RGCC**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Cytokine Panel	**MAYO CLINIC LABORATORIES**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Salivary Cytokine Panel	**SALIMETRICS**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Informational Purpose Test or Platform**
Advanced MethylDetox Profile	**CELL SCIENCE SYSTEMS**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Advanced MethylDetox Profile plus Telomere Length Test	**CELL SCIENCE SYSTEMS**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Genetic Age Test	**CERASCREEN**	PANEL	Healthcare-Ready	**Informational Purpose Test or Platform**

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
AGE-Reader mu Test	**DIAGNOPTICS**	PANEL	Approved for Clinical Use	**Biomarkers Real-Time Assessment Technology** (+5 Availability Weight Points)
GlycanAge Test	**GLYCANAGE**	PANEL	Healthcare-Ready	**Informational Purpose Test or Platform**
Viome Gut Intelligence™ Test	**VIOME**	PANEL	Healthcare-Ready	**Informational Purpose Test or Platform**
SmartGUT™ Microbiome Test	**SMARTDNA**	PANEL	Healthcare-Ready	**Informational Purpose Test or Platform**
Microba Insight™	**MICROBA**	PANEL	Healthcare-Ready	**Informational Purpose Test or Platform**
Gut Microbiota Biohacker	**TFTAK CENTER OF FOOD AND FERMENTATION TECHNOLOGIES**	PANEL	Healthcare-Ready	**Informational Purpose Test or Platform**
Health plus Ancestry Service	**23ANDME**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
Array Comparative Genomic Hybridisation (aCGH) RGCC	**RGCC**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
ImmunoGenomic® Profile	**GENOVA DIAGNOSTICS**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
NeuroGenomic™ Profile	**GENOVA DIAGNOSTICS**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
CardioGenomicPlus™ Profile	**GENOVA DIAGNOSTICS**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
PhysioAge Biomarkers of Aging Test	**PHYSIOAGE**	PANEL	Approved for Clinical Use	**Medical Test** (+2 Availability Weight Points)
DiscoveryMAP v. 3.3 Panel	**MYRIAD RBM**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Explorer MAP™ v. 1.0	**MYRIAD RBM**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
HumanMAP® v. 2.0	**MYRIAD RBM**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
CardiovascularMAP® v. 3.0	**MYRIAD RBM**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
InflammationMAP® v. 1.0	**MYRIAD RBM**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
ImmunoMAP® v. 1.0	**MYRIAD RBM**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
NeuroMAP™ v. 1.0	**MYRIAD RBM**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
MetabolicMAP® v. 1.0	**MYRIAD RBM**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
CytokineMAP A	**MYRIAD RBM**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
CytokineMAP B	**MYRIAD RBM**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
AngiogenesisMAP® v. 1.0	**MYRIAD RBM**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
LEGENDScreen™ Human PE Kit	**BIOLEGEND**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
LEGENDplex™ Human B Cell Panel (13-plex)	**BIOLEGEND**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
LEGENDplex™ Human CD8/NK Panel (13-plex)	**BIOLEGEND**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
LEGENDplex™ Human Th Cytokine Panel (13-plex)	**BIOLEGEND**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Regulatory T-Cell Panel	**ARUP LABORATORIES**	PANEL	Healthcare-Ready	**Medical Test** (+2 Availability Weight Points)
Cytokine Panel	**ARUP LABORATORIES**	PANEL	Healthcare-Ready	**Medical Test** (+2 Availability Weight Points)
Cytokine Panel, TH1	**ARUP LABORATORIES**	PANEL	Healthcare-Ready	**Medical Test** (+2 Availability Weight Points)

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
Carnitine Panel	**ARUP LABORATORIES**	PANEL	Healthcare-Ready	**Medical Test** (+2 Availability Weight Points)
Hepatic Function Panel	**ARUP LABORATORIES**	PANEL	Healthcare-Ready	**Medical Test** (+2 Availability Weight Points)
B-Cell Memory and Naive Panel	**ARUP LABORATORIES**	PANEL	Healthcare-Ready	**Medical Test** (+2 Availability Weight Points)
Natural Killer Cell and Natural Killer T-Cell Panel	**ARUP LABORATORIES**	PANEL	Healthcare-Ready	**Medical Test** (+2 Availability Weight Points)
OMIP-004: In-Depth Characterization of Human T Regulatory Cells	**N/A**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Epidem. or Theoretical Panel Only** (BAI=0; ACTIONAB.=0)
OMIP-007: Phenotypic Analysis of Human Natural Killer Cells	**N/A**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Epidem. or Theoretical Panel Only** (BAI=0; ACTIONAB.=0)
OMIP-018: Chemokine Receptor Expression on Human T Helper Cells	**N/A**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Epidem. or Theoretical Panel Only** (BAI=0; ACTIONAB.=0)
OMIP-027: Functional Analysis of Human Natural Killer Cells	**N/A**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Epidem. or Theoretical Panel Only** (BAI=0; ACTIONAB.=0)
OMIP-029: Human NK-Cell Phenotypization	**N/A**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Epidem. or Theoretical Panel Only** (BAI=0; ACTIONAB.=0)
OMIP-039: Detection and analysis of human adaptive NKG2C+ natural killer cells	**N/A**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Epidem. or Theoretical Panel Only** (BAI=0; ACTIONAB.=0)

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
Cardiometabolic Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Cell Regulation Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Cardiovascular II Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Cardiovascular III Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Immune Response Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Inflammation Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Metabolism Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Neurology Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Neuro Exploratory Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Oncology II Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
Oncology III Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Organ Damage Panel	**OLINK**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Human v3 miRNA Assay	**NANOSTRING**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
MiRXES ID3EAL miRNA Assay	**MiRXES**	PANEL	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
OsteomiRTM - Validated Bone Biomarkers	**TAmiRNA**	PANEL	Healthcare-Ready	**Informational Purpose Test or Platform**
ThrombomiRTM - Biomarkers of Platelet Function	**TAmiRNA**	PANEL	Healthcare-Ready	**Informational Purpose Test or Platform**
ToxomiRTM - Biomarkers of Toxicity	**TAmiRNA**	PANEL	Healthcare-Ready	**Informational Purpose Test or Platform**
DNAge™ Epigenetic Aging Clock	**ZYMO RESEARCH**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**
Epigenetic Age Analysis Version 2.0	**OSIRIS GREEN**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**
DNAge® test	**BIOVIVA**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
EpiHealth	**CHRONOMICS**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**
EpiAging	**HKG EPITHERAPEUTICS**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**
EpiSocialpsych	**HKG EPITHERAPEUTICS**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**
Targeted Sequencing For DNA Methylation Analysis	**HKG EPITHERAPEUTICS**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**
EpiLiver	**HKG EPITHERAPEUTICS**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**
EpiBreast	**HKG EPITHERAPEUTICS**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**
TeloYears plus Advanced Ancestry Tests	**TELOYEARS**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**
Telomere Length and Biological Age Testing	**LIFE LENGTH**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**
Telomere Length Test	**CELL SCIENCE SYSTEMS**	SINGLE BIOMARKER	Healthcare-Ready	**Informational Purpose Test or Platform**
CD4+ T-Cell Recent Thymic Emigrants (RTEs)	**ARUP LABORATORIES**	SINGLE BIOMARKER	Healthcare-Ready	**Medical Test** (+2 Availability Weight Points)

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
CD21 (Dendritic Cell) by Immunohistochemistry	**ARUP LABORATORIES**	SINGLE BIOMARKER	Healthcare-Ready	**Medical Test** (+2 Availability Weight Points)
CD57+ NK Cells, Peripheral Blood by Flow Cytometry	**ARUP LABORATORIES**	SINGLE BIOMARKER	Healthcare-Ready	**Medical Test** (+2 Availability Weight Points)
Phospho-H2AX (Ser139) Cellular Kit	**CISBIO**	SINGLE BIOMARKER	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Senescence Detection Kit	**ABCAM**	SINGLE BIOMARKER	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
SPiDER-ßGal	**DOJINDO MOLECULAR TECHNOLOGIES**	SINGLE BIOMARKER	Research Use Only (-2 Availab. Weight Points)	**Research Kit or OLPS** (Accuracy Index x *RKOLPS coefficient*)
Young.AI	**INSILICO MEDICINE**	DIGITAL PANEL PLATFORM	Healthcare-Ready	**AI Platform** (+5 Availability Weight Points)
Aging.AI	**INSILICO MEDICINE**	DIGITAL PANEL PLATFORM	Healthcare-Ready	**AI Platform** (+5 Availability Weight Points)
PhotoAgeClock	**HAUT.AI**	DIGITAL PANEL PLATFORM	Healthcare-Ready	**AI Platform** (+5 Availability Weight Points)
Haut.AI Skin Health	**HAUT.AI**	DIGITAL PANEL PLATFORM	Healthcare-Ready	**AI Platform** (+5 Availability Weight Points)
AgeMeter	**CENTERS FOR AGE CONTROL**	DIGITAL PANEL PLATFORM	Approved for Clinical Use	**Biomarkers Real-Time Assessment Technology** (+5 Availability Weight Points)

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
Health Reviser Platform	**HEALTH REVISER**	DIGITAL PANEL PLATFORM	Approved for Clinical Use	**Biomarkers Real-Time Assessment Technology** (+5 Availability Weight Points)
MEDIAGE™ Biological Age Measurement System	**MEDIAGE**	DIGITAL PANEL PLATFORM	Approved for Clinical Use	**Biomarkers Real-Time Assessment Technology** (+5 Availability Weight Points)
CarePredict Platform	**CAREPREDICT**	DIGITAL PANEL PLATFORM	Approved for Clinical Use	**AI Platform** (+5 Availability Weight Points)
Enlitic Platform	**ENLITIC**	DIGITAL PANEL PLATFORM	Healthcare-Ready	**AI Platform** (+5 Availability Weight Points)
Freenome Platform	**FREENOME**	DIGITAL PANEL PLATFORM	Research Use Only (-2 Availab. Weight Points)	**AI Platform** (+5 Availability Weight Points)
AI-Powered Radiology Assistant	**ZEBRA MEDICAL VISION**	DIGITAL PANEL PLATFORM	Healthcare-Ready	**AI Platform** (+5 Availability Weight Points)
PathAI Platform	**PATHAI**	DIGITAL PANEL PLATFORM	Healthcare-Ready	**AI Platform** (+5 Availability Weight Points)
Buoy Health Platform	**BUOY HEALTH**	DIGITAL PANEL PLATFORM	Healthcare-Ready	**AI Platform** (+5 Availability Weight Points)
BenevolentAI	**BENEVOLENT**	DIGITAL PANEL PLATFORM	Research Use Only (-2 Availab. Weight Points)	**AI Platform** (+5 Availability Weight Points)
Tempus Platform	**TEMPUS**	DIGITAL PANEL PLATFORM	Research Use Only (-2 Availab. Weight Points)	**AI Platform** (+5 Availability Weight Points)

Selected Biomarker Panels

AGING ANALYTICS AGENCY

NAME	COMPANY or ENTITY	AMPLITUDE LEVEL	CONDITIONING STAGE CATEGORY	OPERATIONAL CATEGORY
KenSci Platform	**KENSCI**	DIGITAL PANEL PLATFORM	Healthcare-Ready	**Biomarkers Real-Time Assessment Technology** (+5 Availability Weight Points)
Proscia Platform	**PROSCIA**	DIGITAL PANEL PLATFORM	Research Use Only (-2 Availab. Weight Points)	**Biomarkers Real-Time Assessment Technology** (+5 Availability Weight Points)
Google's DeepMind Health AI Platform	**DEEPMIND TECHNOLOGIES**	DIGITAL PANEL PLATFORM	Approved for Clinical Use	**AI Platform** (+5 Availability Weight Points)
ICarbonX Platform	**ICARBONX**	DIGITAL PANEL PLATFORM	Research Use Only (-2 Availab. Weight Points)	**AI Platform** (+5 Availability Weight Points)
Blood Chemistry Calculator	**NOURISH BALANCE THRIVE**	DIGITAL PANEL PLATFORM	Healthcare-Ready	**AI Platform** (+5 Availability Weight Points)
Ada - Symptom Checker App	**ADA HEALTH GMBH**	DIGITAL PANEL PLATFORM	Approved for Clinical Use	**AI Platform** (+5 Availability Weight Points)
Babylon Health Platform	**BABYLON HEALTH**	DIGITAL PANEL PLATFORM	Approved for Clinical Use	**AI Platform** (+5 Availability Weight Points)
Digital Nutrition Platform	**ZIPONGO**	DIGITAL PANEL PLATFORM	Healthcare-Ready	**AI Platform** (+5 Availability Weight Points)
Better Therapeutics Platform	**BETTER THERAPEUTICS**	DIGITAL PANEL PLATFORM	Research Use Only (-2 Availab. Weight Points)	**AI Platform** (+5 Availability Weight Points)

Biomarkers of Longevity

Approved for Clinical Use - 41
Research Use Only - 45
Healthcare-Ready - 33

1st edition. Selection and Current Status, 2019

Approved for Clinical Use

Healthcare-Ready
(waiting for clinical approval)

Research Use Only

AGING ANALYTICS AGENCY

Biomarker Panels

InsideTracker Inner Age
InsideTracker Ultimate Plan
aCGH RGCC
Immune-Frame
Comprehensive Adrenal Stress Profile
B-Cell Memory and Naive Panel
Natural Killer Cell and Natural Killer T-Cell Panel
Health + Ancestry Service
Carnitine Panel
Cytokine Panel, TH1
Hepatic Function Panel
Regulatory T-Cell Panel
Cytokine Panel
Adrenal Check
Adrenal Stress Profile
Advanced MethylDetox Profile
Advanced MethylDetox Profile + Thelomere Length
AGE-Reader mu Test
Oxidative Stress Analysis 2.0
Cytokine Panel
Biomarker Panel
Aging Theranostic 1.0
10 Hormone Saliva Test Kit
Anti-Aging #4 Comprehensive Blood and Urine Test Panel
Female/Male Saliva Profile II - Test Kit for 6 Hormone Level Imbalances
Healthy Aging Panel (Comprehensive)
CardioGenomic Plus Profile
ImmunoGenomic Profile
PhysioAge Biomarkers of Aging Test

smartGUT™ Microbiome Test
Genetic Age Test
Viome Gut Intelligence™ Test
Microba Insight™
GlycanAge Test
Gut Microbiota Biohacker
toxomiRTM biomarkers of toxicity
osteomiRTM validated bone biomarkers
thrombomiRTM biomarkers of platelet function

Metabolism Panel
Immune Response Panel
Cardiovascular II Panel
Cell Regulation Panel
Organ Damage Panel
Neurology Panel
Inflammation Panel
Cardiovascular III Panel
Neuro Exploratory Panel
Cardiometabolic Panel
Oncology III Panel
Oncology II Panel
HumanMAP v.2.0
MetabolicMAP v.1.0
CardiovascularMAP v.3.0
DiscoveryMAP v.3.3 Panel
AngiogenesisMAP v.1.0
NeuroMAP v.1.0
ImmunoMAP v.1.0
Explorer MAP v.1.0
InflammationMAP v.1.0
CytokineMAP B
CytokineMAP A
LEGENDplex Human CD8/NK Panel
LEGENDplex Human B Cell Panel
MiRXES ID3EAL miRNA Assay
Phospho-H2AX (Ser139) cellular kit
Senescence Detection Kit
SPIDER-βGal
OMIP-004
OMIP-018
OMIP-039
Salivary Cytokine Panel
LEGENDScreen Human PE Kit
LEGENDplex Human Th Cytokine Panel
OMIP-027
OMIP-007
OMIP-029
Human v3 miRNA Assay

Digital Panel Platforms

Babylon Health Platform
Ada
Symptom Checker app
CarePredict Platform
Health Reviser Platform
Google's DeepMind Health AI Platform
Centers for Age Control
AgeMeter

Blood Chemistry Calculator
AI-Powered Radiology Assistant
MEDIAGE™ Biological Age Measurement System
KenSci Platform
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Buoy Health Platform
PhotoAgeClock
Haut.AI Skin Health
Digital Nutrition Platform

Proscia Platform
Freenome Platform
BenevolentAI Platform
Better Therapeutics Platform
Tempus Platform
ICabonX Platform

Single Biomarkers

CD4+ T-Cell Recent Thymic Emigrants
CD57+ NK Cells, Peripheral Blood by Flow Cytometry
CD21 (Dendritic Cell) by Immunohistochemistry

Telomere Length Test
DNAge™ Epigenetic Aging Clock
EpiHealth
DNAge® Test
EpiLiver
TeloYears + Advanced Ancestry Tests
Epigenetic Age Analysis Version 2.0
EpiAging
EpiSocialpsych
Targeted Seq. for DNA Methylation Analysis
Telomere Length and Biological Age Testing
EpiBreast

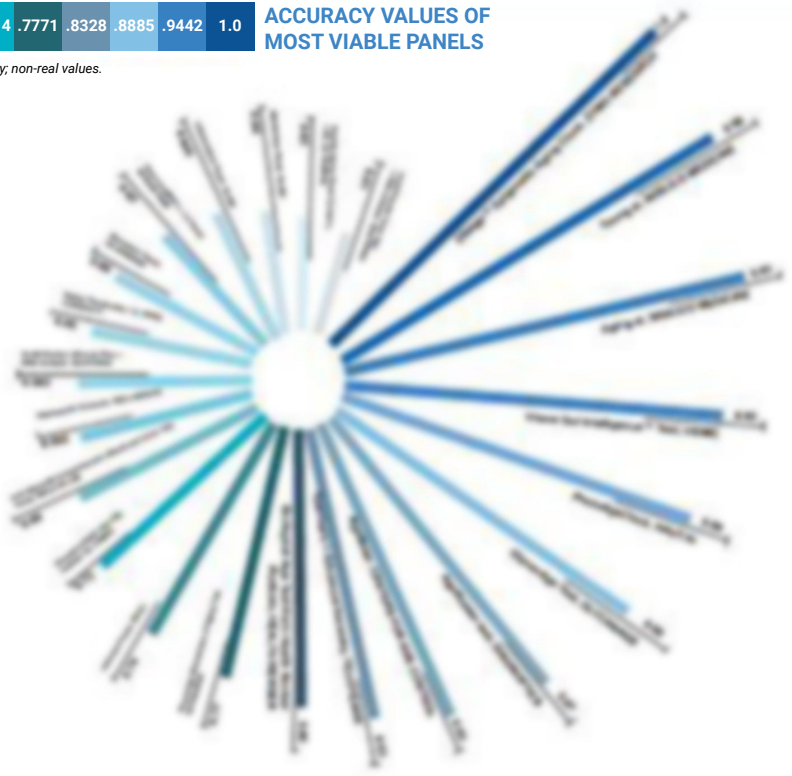
Most Viable Panels: Coming Soon

AGING ANALYTICS AGENCY

.6657 .7214 .7771 .8328 .8885 .9442 1.0

ACCURACY VALUES OF MOST VIABLE PANELS

Illustrative only; non-real values.



3.82 4.85 5.88 6.91 7.94 8.97 10

AVAILABILITY VALUES OF MOST VIABLE PANELS

Illustrative only; non-real values.

It is Aging Analytics Agency's hope that our comparative analytics framework and methodology will serve as a useful long-term analytical tool for aging single biomarkers and panels assessment to identify the most advanced, available and actionable resources to create, manage, optimize and improve action plans for the health and Longevity industry, market and public sectors.

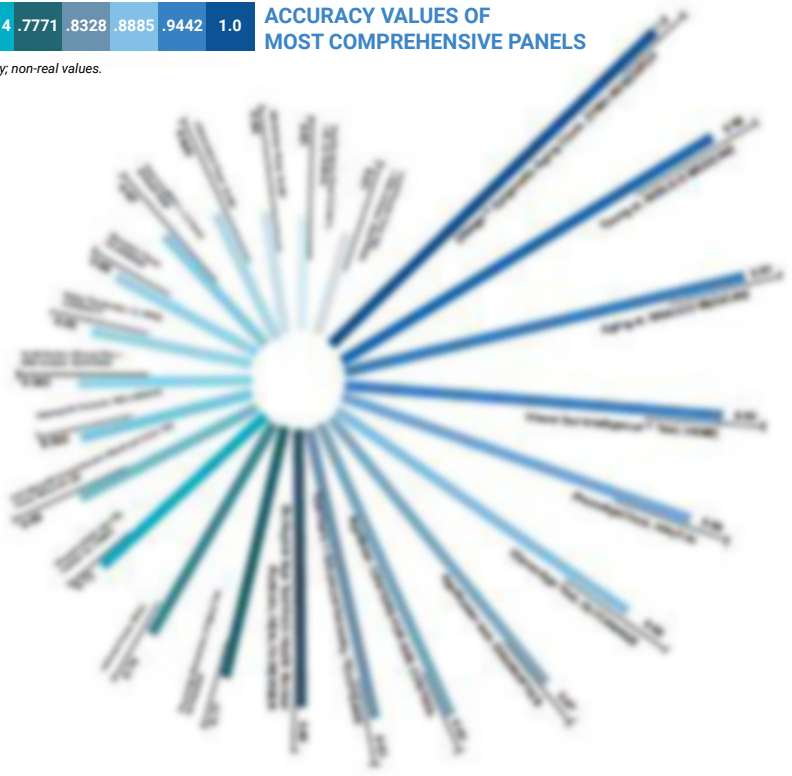
Most Comprehensive Panels

AGING ANALYTICS AGENCY

.6657 .7214 .7771 .8328 .8885 .9442 1.0

ACCURACY VALUES OF MOST COMPREHENSIVE PANELS

Illustrative only; non-real values.



3.82 4.85 5.88 6.91 7.94 8.97 10

AVAILABILITY VALUES OF MOST COMPREHENSIVE PANELS

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It is Aging Analytics Agency's hope that our comparative analytics framework and methodology will serve as a useful long-term analytical tool for aging single biomarkers and panels assessment to identify the most advanced, available and actionable resources to create, manage, optimize and improve action plans for the health and Longevity industry, market and public sectors.

Conclusions

Conclusions

The use of biomarkers is an indispensable component of industry analytics and assessment. It is the foundation upon which measurement of Healthy Longevity and the effectiveness of P4 (Precision, Preventive, Personalized, Participatory) Medicine and Longevity therapeutics is built. This special analytical case study is designed as an in-depth review of the state of the art in biomarkers of biological age to advise private and public sector participants effectively.

It was produced to offer a panoramic review of the global landscape of aging and Longevity biomarkers, containing selected lists, rankings and enhanced profiles of more than 50 single biomarkers directly correlated with the trajectories of age-related diseases and syndromes, and exceeding 100 diverse biomarker panels for analytical data-driven comparisons that allow for an optimal integration of multiple biomarkers for practical use, achieving highly actionable monitoring systems for healthcare, clinical practice, translational research, frontier developments that exploit the current conditions of the rising Longevity industry, and the execution of public policies aiming to increase National Healthy Longevity that will result in a renaissance never seen before in economic and social dynamics.

In addition to their purely descriptive and analytical approaches, the report is designed to make key strategic recommendations, and to offer guidance regarding biomarker implementations, technologies and techniques within the reach of companies and nations today, in order to equip them with the tools necessary for optimizing their strategy and action plans, providing specialized guidelines for business, investment and policy decision making. The report delivers a most comprehensive list of single biomarkers and biomarker panels of biological age together with extensive and enhanced profiles: their advantages, disadvantages, future perspectives, challenges and opportunities, with a focus on technologies currently used for assessment; concrete analysis of routine, advanced and novel biomarkers of aging, emerging tools and platforms, and insights about the impact of these biomarkers on health systems and clinical practice. A special treatment tracing the role of Digital Biomarkers and AI platforms as necessary and indispensable components of the Longevity biomarker industry is also delivered, highlighting the fact that AI and data science are increasingly necessary to handle the increasing volume of biomarker, life and health data.

Conclusions

The report's central conclusion is that as the scope of P4 Medicine broadens actively and healthily, the number of biomarkers, measurement technologies and platforms will increase rapidly to the thousands in the coming years. This will provide the opportunity to improve medical stratification to its maximum degree, enabling the adoption of Personalized, Participatory, Precision and Preventive Medicine for both the young, the middle aged and the old.

This will also enable the conditions necessary for conducting more exhaustive and precise studies with samples of only one individual, and a shift away from testing therapies using conventional model organisms and toward a more human-centered approach, due to the enormous flow of biological digital data that will be extracted continuously, individual to individual.

These vast amounts of continuous biomarker data will make impractical the implementation of P4 Medicine by current, manual means without the use of AI and advanced data science techniques and technologies.

Aggregation of biomarkers of Longevity, rather than biomarkers of disease only, and from healthy populations (e.g. the young, middle aged and healthy elderly), rather than bedside data from hospital populations, will be part of everyday life due to the novel digital health platforms capable of extracting truly massive amounts of relevant clinical data from single patients.

It is impossible to determine whether biotechnologies for Longevity have been successful if we cannot tell how advanced the aging process is in any given individual; but at the same time the latter will not be feasible until successfully achieving highly actionable panels that allow for evaluating the aging process in broad healthy and less healthy differentiated ranges of the population spectrum.

It in this sense that biomarkers are an essential factor in 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 important to develop and promote the widespread use of a panel of biomarkers that is precise enough and immediately actionable.

The report documents many aging biomarkers, and identifies from among them those which, by the metrics described (and which have never been reported in pre existing literature), belong to the category we have named Minimum Required: the Most Viable Products for immediate implementation.

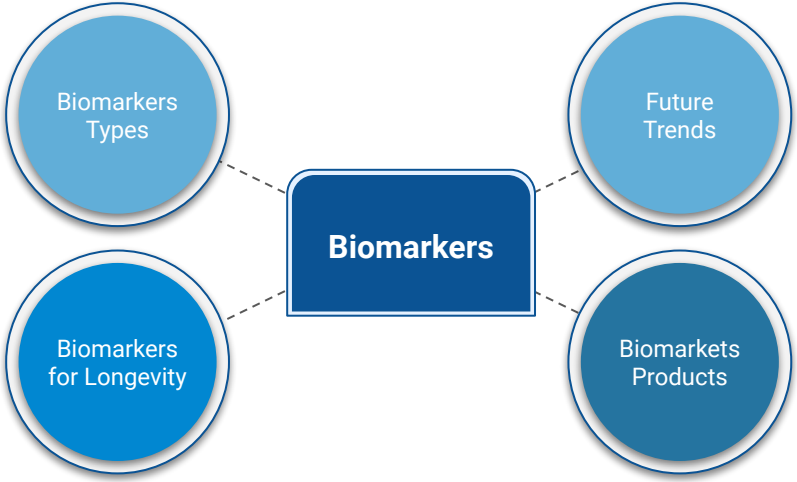
It is our hope and commitment that regardless of whether it is adopted wholesale, the results of the report's analysis can guide relevant counterparties on how to optimally utilize existing technologies to maximize the health of aging populations and aging economies, as soon as possible.

Conclusions

- Biomarkers of Physical Function and Physiology
- Blood-based biomarkers
- Cognitive biomarkers

Emergence on integrative platforms and complex biomarker analysis tools

- The number of biomarkers, measurement technologies and platforms will increase rapidly to the thousands in the coming years.
- This will provide the opportunity to improve medical stratification to its maximum degree, enabling the adoption of Personalized, Participatory, Precision and Preventive Medicine for both the young, the middle aged and the old.
- This will also enable the conditions necessary for conducting more exhaustive and precise studies with samples of only one individual, and a shift away from testing therapies using conventional model organisms to a more human approach.



- Prediction
- Prevention
- Personalization
- Participation
- Diagnostics

Novel applications in medicine and integration with other biotech sectors

- Biomarker panels
- Digital biomarker platforms
- Single biomarkers

Major Deliverables and Conclusions

1. **What are the current most comprehensive biomarkers and panels to follow the aging trajectory and its related conditions and the most viable or minimum required ones, and how they can be implemented in the most ideal and useful manner?**
2. **What leading personalised and preventive market-ready health assessments can aging biomarkers and panels bring to the existing pipeline of healthcare entities to maximize their competitive advantage?**
3. **What novel updates and advances in biomarker-related research and development will impact the health industry in the next years? Which of those should be watched closely for integration into clinics and biomedical or healthcare companies' existing pipelines as soon as their conditioning is achieved?**

We feel that our efforts over the course of the past five years have established a solid foundation of knowledge and expertise upon which we intend to summarize the entire landscape of aging and Longevity biomarker utilities in the health industry: the production of this new report entitled ***Biomarkers of Longevity Landscape Overview 2019: Current State, Challenges and Opportunities.***

This upcoming version will be a +300 page report aiming to answer these three specific questions, to be produced over the next 3-6 months, with a new edition of this report during each financial quarter, incrementally increasing its breadth and depth as we go along, and with each edition providing a deeper, more comprehensive and more precise understanding of the landscape. It will deliver:

- Concrete deep analysis of which biomarkers and biomarker panels are available today, its strengths and weaknesses, their accuracy, availability and current actionability, and the opportunities and challenges related to its uses for real-time and precision monitoring of health status, and ultimately the reversal of biological age;
- Tangible estimations of which biomarkers of aging, health and Longevity are market ready and at the stage of development necessary for precision assessment of health status and endpoints of clinical trials and therapies;
- Highlights regarding the role of digital biomarkers and AI platforms and how they will become necessary and indispensable components of aging and Longevity biomarker discovery, research, development and practical use.

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ANALYTICS
AGENCY

Link to the Report: www.aginganalytics.com/biomarkers-of-longevity

E-mail: info@aginganalytics.com | **Website: www.aginganalytics.com**