THE 12 HALLMARKS OF AGING

A systems view of the human body

What changes over time, why it matters, and how it all connects.

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Aging is not one thing.

It's a system.

No single pathway breaks down on its own.

Over time, changes build across DNA, mitochondria, proteins, cellular cleanup, metabolism, immune signaling, the microbiome, and more.

The important part isn't that there are twelve hallmarks.
It's that they interact.

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The 12 Hallmarks at a Glance

PRIMARY HALLMARKS

Sources of cellular damage

01 Genomic Instability

Accumulating damage to DNA and the systems responsible for maintaining it.

02 Telomere Attrition

Changes to the protective structures at the ends of chromosomes.

03 Epigenetic Alterations

Age-related changes in how genes are regulated and expressed.

04 Loss of Proteostasis

Declining ability to correctly make, fold and clear proteins.

05 Disabled Macroautophagy

Reduced efficiency of cellular recycling and damaged-component removal.

ANTAGONISTIC HALLMARKS

Responses that can become harmful when persistent

06 Deregulated Nutrient Sensing

Disruption of pathways that coordinate nutrients, energy, growth and repair.

07 Mitochondrial Dysfunction

Changes in cellular energy production, signaling and mitochondrial quality control.

08 Cellular Senescence

Damaged or stressed cells stop dividing while remaining metabolically active.

INTEGRATIVE HALLMARKS

System-level consequences of accumulated dysfunction

09 Stem Cell Exhaustion

Declining capacity to replenish and repair tissues.

10 Altered Intercellular Communication

Disrupted signaling between cells, tissues and organs.

11 Chronic Inflammation

Persistent low-grade inflammatory signaling.

12 Dysbiosis

Age-related changes in microbial ecosystems and host-microbe interactions.

Twelve hallmarks. ***One interconnected system.***

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Hallmarks of Aging Framework

The Hallmarks of Aging are twelve biological processes scientists use to map how aging unfolds. They are grouped by role: sources of damage, responses that amplify it, and the system-wide effects that follow.

Cause

Primary

Antagonistic

Integrative

Consequence

Initiating Damage

Where Cellular Wear Begins

GENOMIC INSTABILITY

TELOMERE ATTRITION

EPIGENETIC ALTERATIONS

LOSS OF PROTEOSTASIS

DISABLED MACROAUTOPHAGY

Amplifying Response

Beneficial at Low Levels, Harmful When Chronic

DEREGULATED NUTRIENT SENSING

MITOCHONDRIAL DYSFUNCTION

CELLULAR SENESCENCE

System-Level Failure

Downstream Effects on Tissues and Organs

STEM CELL EXHAUSTION

ALTERED INTERCELLULAR COMMUNICATION

CHRONIC INFLAMMATION

DYSBIOSIS

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Framework: López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. *Cell*. 2023;186(2):243-278.

PRIMARY HALLMARK

01

Genomic Instability

Your cellular instruction manual accumulates damage.

THINK OF IT LIKE

The Missing Instructions

Your DNA is the instruction manual for your cells. Over time it collects errors. Picture a furniture manual with missing steps: the final product will not come together the way it should.

IN PLAIN ENGLISH

Your DNA is constantly exposed to damage from normal metabolism, replication, environmental stress and other sources.

Cells have sophisticated repair systems, but damage and repair errors accumulate over time.

WHY IT MATTERS

DNA contains the instructions cells use to function. When damage builds faster than it can be repaired, cells may lose function, enter senescence or activate other stress responses.

WHAT INFLUENCES IT

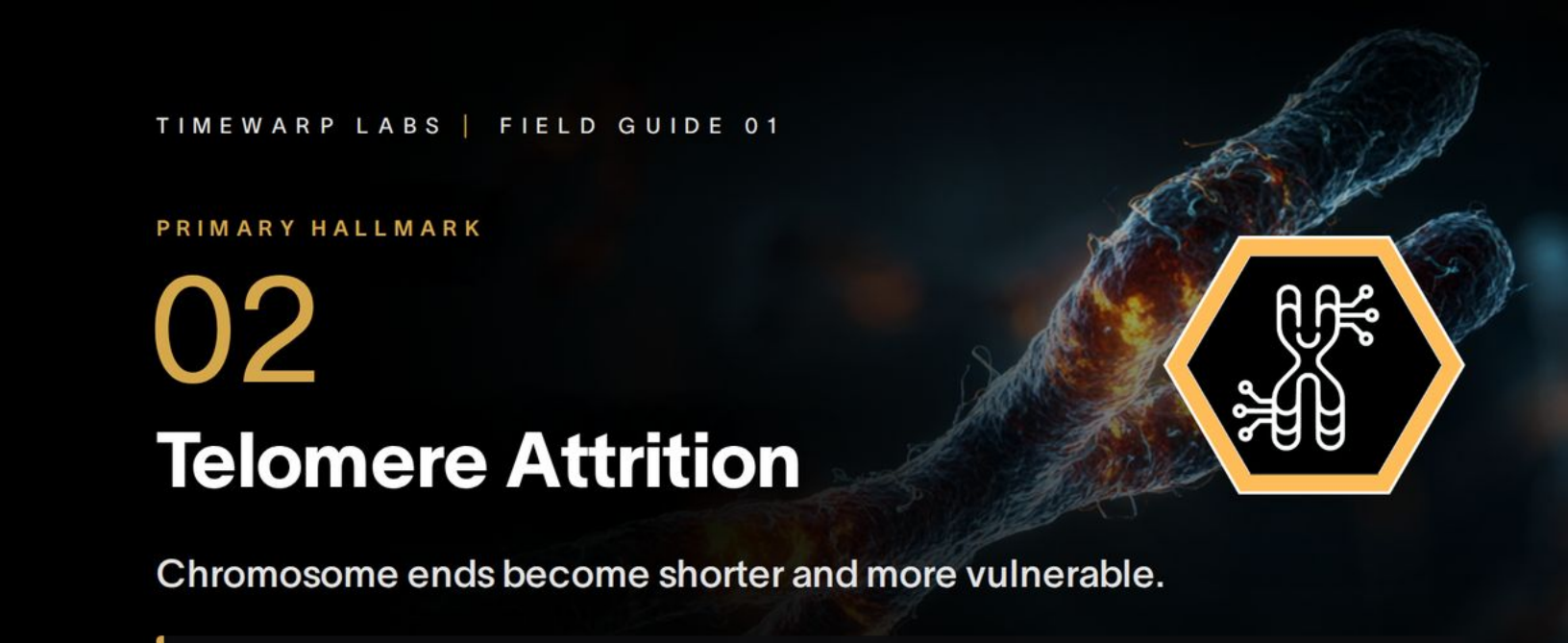
- DNA replication
- Oxidative stress
- UV and ionizing radiation
- Environmental exposures
- DNA repair capacity

RESEARCHERS ARE STUDYING

- DNA repair pathways
- Genome maintenance
- Oxidative damage
- Mitochondrial DNA integrity
- Cellular stress responses

CONNECTED TO

Senescence | Mitochondria | Epigenetics | Inflammation



PRIMARY HALLMARK

02

Telomere Attrition

Chromosome ends become shorter and more vulnerable.

THINK OF IT LIKE

The Fraying Shoelace

Telomeres work like the plastic tips on shoelaces, protecting the ends of your chromosomes. They tend to get shorter each time a cell divides. When they get too short, the cell reads the ends as damage and stops dividing.

IN PLAIN ENGLISH

Telomeres are protective structures at the ends of chromosomes.

They tend to shorten as cells divide, and critically short or damaged telomeres can trigger a DNA-damage response.

WHY IT MATTERS

Telomere dysfunction can limit cellular replication and contribute to senescence or loss of tissue-renewal capacity.

But longer is not automatically better. Telomere maintenance must be tightly regulated, particularly because uncontrolled cell replication is also a feature of cancer.

WHAT INFLUENCES IT

- Cell division
- Oxidative stress
- Inflammation
- DNA repair
- Telomerase activity

RESEARCHERS ARE STUDYING

- Telomerase biology
- Telomere maintenance
- Cellular stress
- Tissue-specific telomere dynamics

CONNECTED TO

Genomic Instability | Senescence | Stem Cells | Inflammation

PRIMARY HALLMARK

03

Epigenetic Alterations

The DNA sequence can stay the same while the instructions change.

THINK OF IT LIKE

The Broken Light Switch

Your genes are like thousands of switches that control when functions turn on and off. With age these switches get faulty. Some stay on when they should be off. Others fail to turn on at all.

IN PLAIN ENGLISH

Cells regulate which genes are switched on or off through mechanisms layered on top of the DNA sequence.

These patterns change with age.

WHY IT MATTERS

Epigenetic changes can alter gene expression, cellular identity and the way cells respond to stress.

Some biological-age measurements use age-associated epigenetic patterns as biomarkers.

WHAT INFLUENCES IT

- DNA methylation
- Histone modifications
- Chromatin structure
- Metabolism
- Environmental exposures

RESEARCHERS ARE STUDYING

- Epigenetic clocks
- Cellular reprogramming
- Chromatin remodeling
- Gene-regulation stability

CONNECTED TO

Genomic Instability | Nutrient Sensing | Stem Cells | Mitochondria

PRIMARY HALLMARK

04

Loss of Proteostasis

Cellular quality control becomes less reliable.

THINK OF IT LIKE

Clogged Cell Machinery

Proteins are tiny machines that keep your cells running. With age, damaged or misshapen proteins pile up like broken machines on a factory floor. The whole factory slows down.

IN PLAIN ENGLISH

Cells constantly make, fold, repair and remove proteins.

With age, the systems responsible for keeping proteins functional can become less effective.

WHY IT MATTERS

Misfolded or damaged proteins can accumulate, disrupt normal cellular function and place additional stress on repair and recycling systems.

WHAT INFLUENCES IT

- Protein folding
- Molecular chaperones
- Proteasomal degradation
- Cellular stress
- Autophagy

RESEARCHERS ARE STUDYING

- Protein quality control
- Chaperone activity
- Proteasome function
- Protein aggregation

CONNECTED TO

Autophagy | Mitochondria | Inflammation | Nutrient Sensing

PRIMARY HALLMARK

05

Disabled Macroautophagy

The cell's recycling system becomes less efficient.

THINK OF IT LIKE

The City Without Trash Collection

Autophagy is the body's recycling program. Cells break down and reuse old parts to stay efficient. With age this system slows, like a city where the garbage trucks stop coming. Waste piles up.

IN PLAIN ENGLISH

Autophagy helps cells break down and recycle damaged proteins, organelles and other cellular material.

This recycling capacity can decline with age.

WHY IT MATTERS

When damaged components are not efficiently removed, cellular stress can rise and dysfunctional material can accumulate.

Autophagy also influences metabolism, immunity and cellular signaling.

WHAT INFLUENCES IT

- Nutrient availability
- Cellular energy status
- Lysosomal function
- Stress signaling
- Mitochondrial quality control

RESEARCHERS ARE STUDYING

- Autophagy activation
- Lysosomal health
- Mitophagy
- Nutrient-sensing pathways

CONNECTED TO

Proteostasis | Mitochondria | Nutrient Sensing | Inflammation

ANTAGONISTIC HALLMARK

06

Deregulated Nutrient Sensing

Cells become less effective at balancing growth, energy and repair.

THINK OF IT LIKE

The Broken Thermostat

Nutrient-sensing pathways act like a thermostat for energy, deciding when to grow, conserve or repair. With age the thermostat drifts, and cells misread nutrient signals.

IN PLAIN ENGLISH

Cells constantly sense nutrient and energy availability.

Pathways including mTOR, AMPK, insulin/IGF-1 signaling and sirtuins help determine whether cells prioritize growth, maintenance or repair.

WHY IT MATTERS

With age, this coordination can become less precise.

That can affect metabolism, cellular cleanup, mitochondrial function and stress resistance.

KEY SYSTEMS

- mTOR
- AMPK
- Insulin / IGF-1
- Sirtuins
- NAD-related metabolism

RESEARCHERS ARE STUDYING

- Caloric restriction biology
- Fasting-related pathways
- mTOR modulation
- AMPK activation
- Metabolic flexibility

CONNECTED TO

Autophagy | Mitochondria | Proteostasis | Epigenetics

ANTAGONISTIC HALLMARK

07

Mitochondrial Dysfunction

The systems that produce and manage cellular energy change with age.

THINK OF IT LIKE

The Fading Batteries

Mitochondria are your cells' batteries, powering movement, thinking and repair. With age they can hold less charge and give off more reactive byproducts, like a battery that starts to leak.

IN PLAIN ENGLISH

Mitochondria do far more than produce ATP.

They also participate in signaling, metabolism, stress responses and cell survival.

WHY IT MATTERS

Age-related changes can affect mitochondrial efficiency, quality control, DNA integrity and communication with the rest of the cell.

Importantly, mitochondrial stress is not always harmful. Some stress signals trigger adaptive responses.

WHAT INFLUENCES IT

- Energy demand
- Mitophagy
- Oxidative signaling
- Mitochondrial DNA
- Metabolic health

RESEARCHERS ARE STUDYING

- Mitophagy
- Mitochondrial biogenesis
- Metabolic flexibility
- Mitochondrial signaling

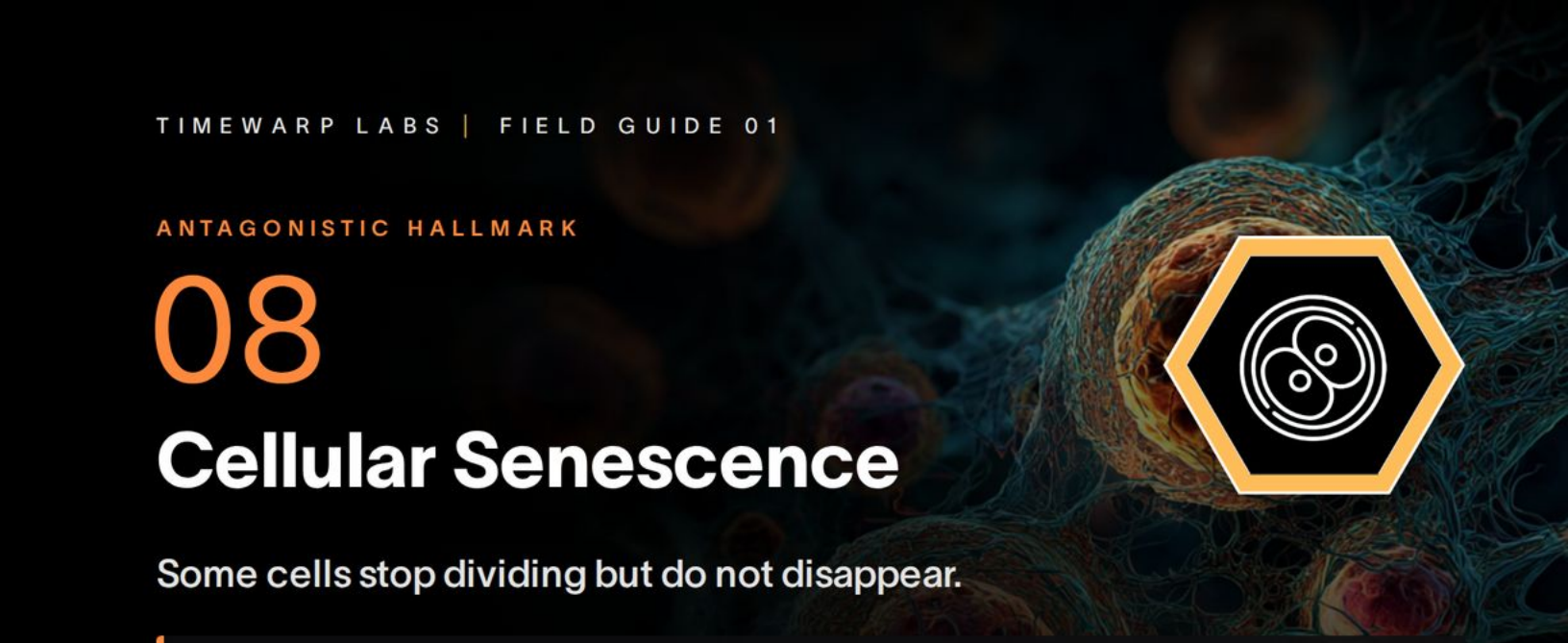
CONNECTED TO

Autophagy | Senescence | Inflammation | Nutrient Sensing

ANTAGONISTIC HALLMARK

08

Cellular Senescence



Some cells stop dividing but do not disappear.

THINK OF IT LIKE

The Bad Neighbors

Some cells stop dividing but do not clear out. They linger like bad neighbors, sending inflammatory signals into the tissue around them.

IN PLAIN ENGLISH

Senescent cells are cells that have entered a stable state in which they no longer divide.

They can remain metabolically active and release signaling molecules into surrounding tissue.

WHY IT MATTERS

Senescence is not inherently harmful. It contributes to tumor suppression, wound healing and normal tissue responses.

The problem may arise when senescent cells accumulate and persist.

WHAT INFLUENCES IT

- DNA damage
- Telomere dysfunction
- Oxidative stress
- Mitochondrial dysfunction
- Immune clearance

RESEARCHERS ARE STUDYING

- Senolytics
- Senomorphics
- Immune-mediated clearance
- SASP signaling

CONNECTED TO

Inflammation | Telomeres | Mitochondria | Stem Cells

INTEGRATIVE HALLMARK

09

Stem Cell Exhaustion

The body's reserve for repair and regeneration declines.

THINK OF IT LIKE

The Retired Workforce

Stem cells are the body's repair crew, ready to replace damaged cells. With age the crew shrinks and becomes less capable, leaving fewer workers to fix the damage.

IN PLAIN ENGLISH

Stem cells help replenish cells throughout the body.

With age, some stem-cell populations decline in number, function or regenerative potential.

WHY IT MATTERS

Reduced stem-cell capacity can impair tissue maintenance, repair and recovery.

Different tissues age differently, so stem-cell exhaustion does not occur uniformly across the body.

WHAT INFLUENCES IT

- DNA damage
- Cellular environment
- Inflammatory signaling
- Metabolism
- Replicative history

RESEARCHERS ARE STUDYING

- Stem-cell preservation
- Tissue regeneration
- Cellular niches
- Regenerative signaling

CONNECTED TO

Senescence | Inflammation | Epigenetics | Telomeres

INTEGRATIVE HALLMARK

10

Altered Intercellular Communication

Aging changes not only the cells, but the messages between them.

THINK OF IT LIKE

Static on the Line

Cells need clear communication to stay in sync, like radios tuned to the same frequency. With age the signals get scrambled, creating static that confuses cells and organs.

IN PLAIN ENGLISH

Cells constantly communicate with one another through hormones, immune signals, neurotransmitters and other molecular messages.

That communication changes with age.

WHY IT MATTERS

Even healthy cells depend on signals from surrounding tissues and systems.

When communication becomes distorted, coordination across organs and tissues can decline.

WHAT INFLUENCES IT

- Hormonal signaling
- Immune signaling
- Neural communication
- Circulating factors
- Local tissue environment

RESEARCHERS ARE STUDYING

- Immune communication
- Endocrine signaling
- Circulating factors
- Tissue-to-tissue signaling

CONNECTED TO

Inflammation | Dysbiosis | Senescence | Stem Cells

INTEGRATIVE HALLMARK

11

Chronic Inflammation

The immune system can shift toward persistent low-grade signaling.

THINK OF IT LIKE

The Smoldering Fire

Inflammation is useful in short bursts. It heals cuts and fights infections. With age the body can slip into constant low-grade inflammation, like a fire that never fully goes out.

IN PLAIN ENGLISH

Inflammation is an essential part of defense and repair.

With age, inflammatory signaling can become more persistent even when there is no acute infection or injury. This is often called inflammaging.

WHY IT MATTERS

Chronic inflammatory signaling can disrupt tissue function and amplify other forms of cellular stress.

It can also be driven by other hallmarks, creating feedback loops.

WHAT INFLUENCES IT

- Immune aging
- Senescent cells
- Metabolic health
- Microbiome changes
- Cellular damage

RESEARCHERS ARE STUDYING

- Immune regulation
- Senescence-associated signaling
- Inflammatory pathways
- Resolution of inflammation

CONNECTED TO

Senescence | Dysbiosis | Mitochondria | Intercellular Communication

INTEGRATIVE HALLMARK

12

Dysbiosis

The microbial ecosystems living with us change too.

THINK OF IT LIKE

The Unbalanced Ecosystem

Your gut hosts trillions of microbes that work like a rainforest ecosystem. With age the balance can shift: some helpful species decline while others overgrow.

IN PLAIN ENGLISH

The body hosts vast communities of microorganisms, particularly in the gut.

Their composition, function and interactions with the host can change with age.

WHY IT MATTERS

Microbes produce metabolites and interact with immune, metabolic and barrier systems throughout the body.

Microbiome changes may therefore influence biology far beyond the gut.

WHAT INFLUENCES IT

- Diet
- Medications
- Environment
- Immune function
- Gut-barrier integrity

RESEARCHERS ARE STUDYING

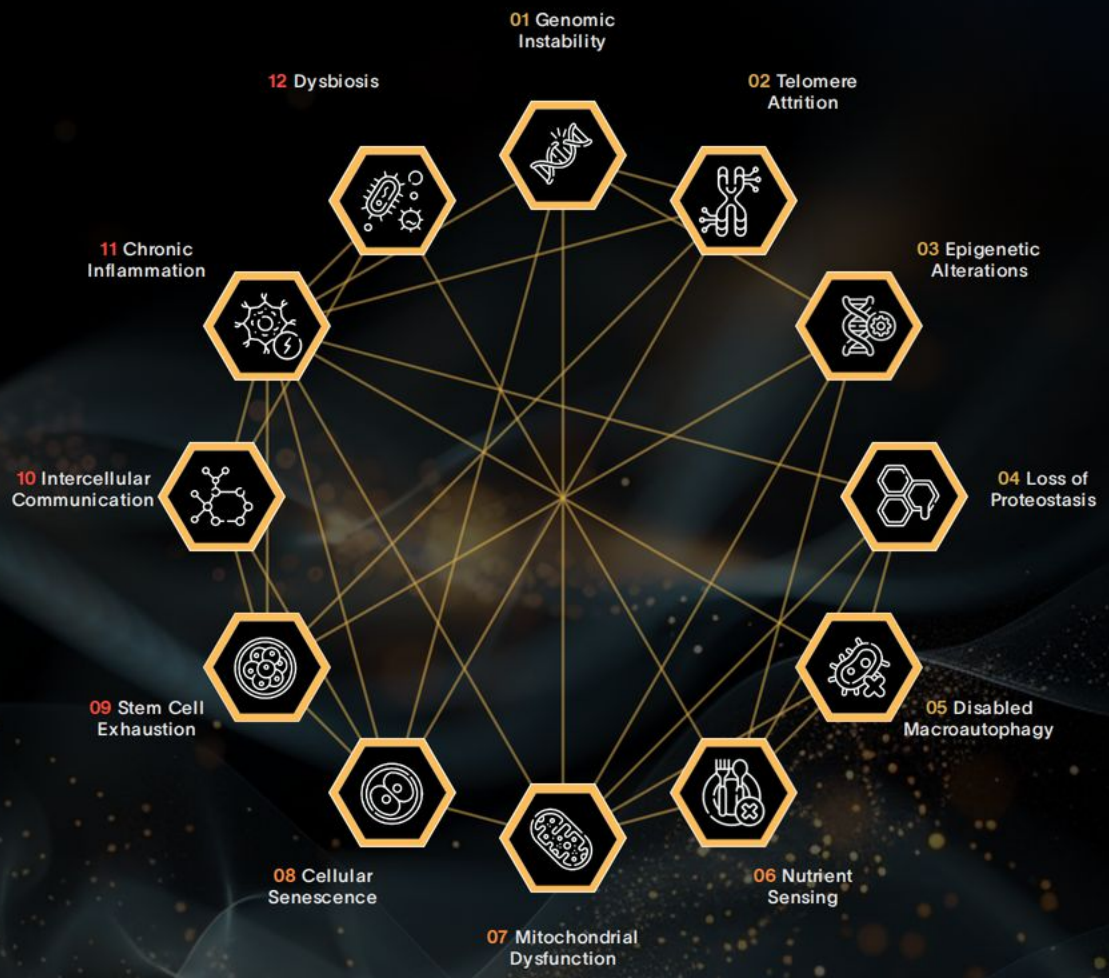
- Microbial diversity
- Microbial metabolites
- Gut-barrier function
- Host-microbe communication

CONNECTED TO

Inflammation | Nutrient Sensing | Immunity | Intercellular Communication

Aging Is a Network

The Hallmarks do not operate independently. Each line below is one of the connections described in this guide. Change one system and the effects travel.



30 connections across 12 hallmarks

ONE LOOP, FOR EXAMPLE

Mitochondrial dysfunction → Cellular stress → Cellular senescence → Inflammatory signaling → Chronic inflammation

which drives further mitochondrial stress

You do not age one pathway at a time.

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WHAT INFLUENCES THE SYSTEM

A Day in Your System

Aging biology is shaped by genetics, environment, behavior and time. Everyday moments touch several hallmarks at once. Here is where researchers look.

MORNING

Light and waking

Morning light helps set your circadian clock, which times metabolism, repair and sleep.

Gene regulation · Metabolism · Cellular repair

DAYTIME

Movement

Researchers study physical activity for its effects on energy production, nutrient signaling and inflammation.

Mitochondria · Nutrient sensing · Inflammation · Proteostasis

MEALS

Nutrition

What you eat feeds the pathways that sense nutrients, and the microbes that live in your gut.

Nutrient sensing · Microbiome · Autophagy · Metabolism

WORKDAY

Stress

Persistent stress shifts the hormone and immune signals that coordinate the whole body.

Intercellular communication · Inflammation · Metabolism

OUTSIDE

Sun and air

UV exposure, smoke and pollutants add to DNA damage and oxidative stress.

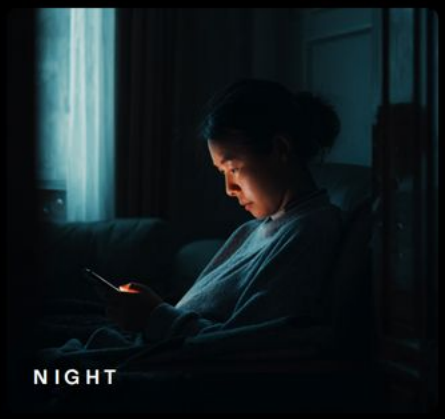
Genomic instability · Senescence · Inflammation

NIGHT

Screens and sleep

Late light and short sleep can push your internal clock off schedule. Sleep is studied for its links to metabolism, inflammation and repair.

Metabolism · Inflammation · Cellular repair



Influencing a pathway does not automatically mean slowing human aging or extending lifespan. The strength of evidence differs substantially across interventions.

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The Research Frontier

Scientists are testing ways to influence many parts of aging biology. Some approaches have substantial evidence for specific health outcomes. Others remain experimental.

01
Senescent-cell targeting
Removing or altering the behavior of persistent senescent cells.

02
Autophagy enhancement
Supporting cellular recycling and quality control.

03
Nutrient-sensing pathways
Modulating pathways such as mTOR, AMPK and insulin/IGF-1.

04
Mitochondrial quality control
Improving mitochondrial maintenance, turnover and signaling.

05
Epigenetic reprogramming
Investigating whether aspects of cellular identity can be restored.

06
Stem-cell preservation
Maintaining regenerative capacity.

07
Immune rejuvenation
Improving age-related changes in immune function.

08
Microbiome modulation
Changing microbial ecosystems or their metabolites.

09
Telomere biology
Understanding telomere maintenance without compromising cellular safeguards.

"Targets a hallmark" is not the same as "proven to slow aging in humans."

Don’t start with the ingredient. Start with the system.

Most longevity conversations begin with a molecule, supplement or intervention. The Hallmarks framework suggests a more useful starting point.

ASK

01 What biological process are we trying to influence?

02 How strong is the evidence?

03 What other systems does it interact with?

04 Are we addressing one pathway repeatedly while ignoring others?

A systems view does not make longevity simple. It makes the complexity visible.

Aging biology is interconnected.
A longevity strategy should be too.

Where do your patterns intersect with the system?

Understanding the Hallmarks is one thing.

Seeing how your own habits and lifestyle patterns relate to the framework is another.

THE LONGEVITY SYSTEMS ASSESSMENT

A short assessment designed to map lifestyle patterns across the biology of aging.

Your answers cannot tell us exactly what is happening inside each cellular pathway. They can help identify areas of relative strength, exposure and opportunity across the Hallmarks framework.

12 QUESTIONS

12 HALLMARKS

1 SYSTEMS-LEVEL VIEW

TAKE THE FREE LONGEVITY SYSTEMS ASSESSMENT

timewarp.com/pages/assessment

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Built From the Science

PRIMARY FRAMEWORK

López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. *Cell*. 2023;186(2):243-278.

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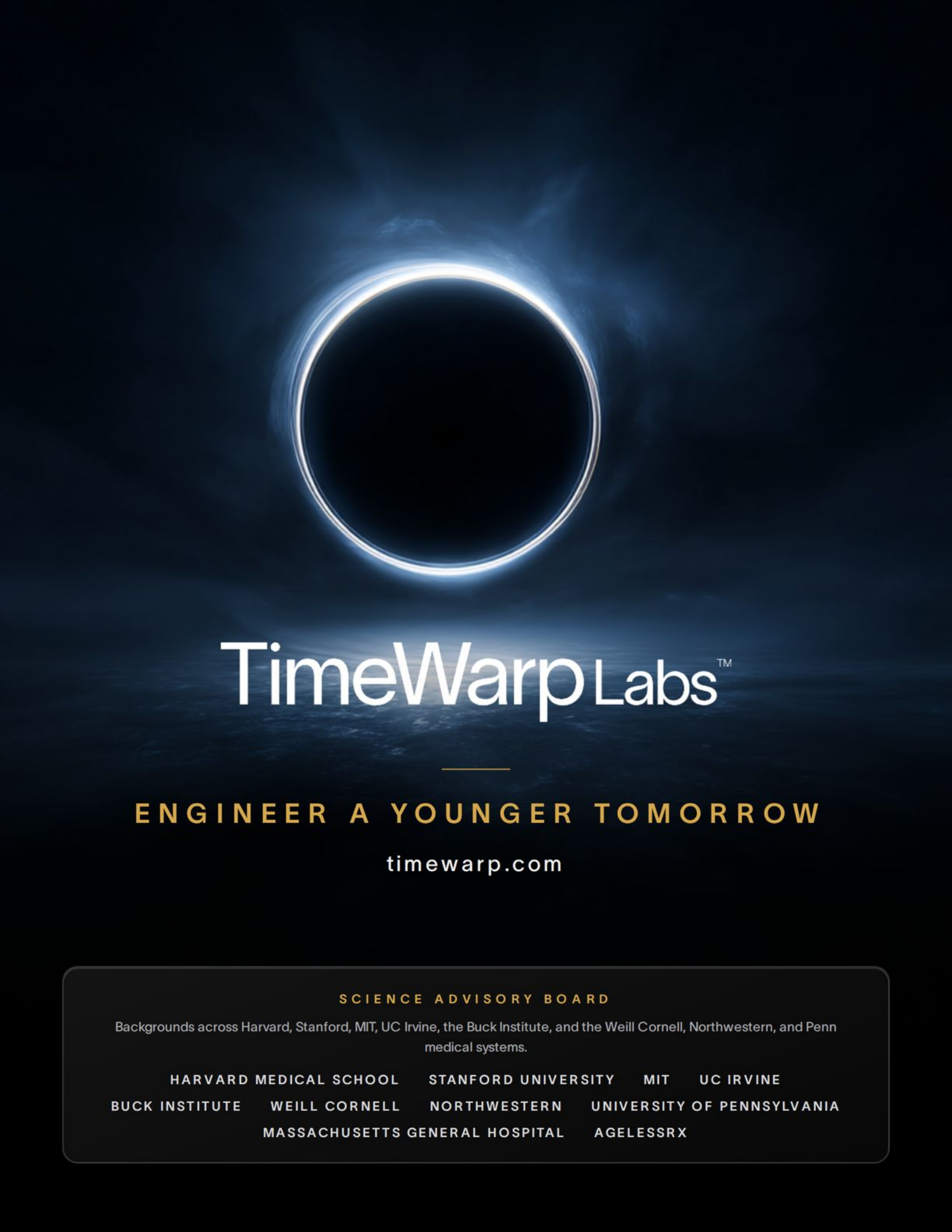

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