On Our Understanding of Aging, Personalized Medicine and Geriatric Care

भारतीय प्रौद्योगिकी संस्थान हैदराबाद
Indian Institute of Technology Hyderabad

G. Narahari Sastry

Fifth Paradigm Lab , Department Biotechnology

Indian Institute of Technology Hyderabad

20th October, 2025

XXXI Symposium on Bioinformatics and Computer-Aided Drug Discovery, Russia

Out line of the presentation

1.
   - Aging, but let’s have a look at health and how it is related to aging

2.
   - Personalized medicine, understanding the differential disease pathophysiology and progrnosis

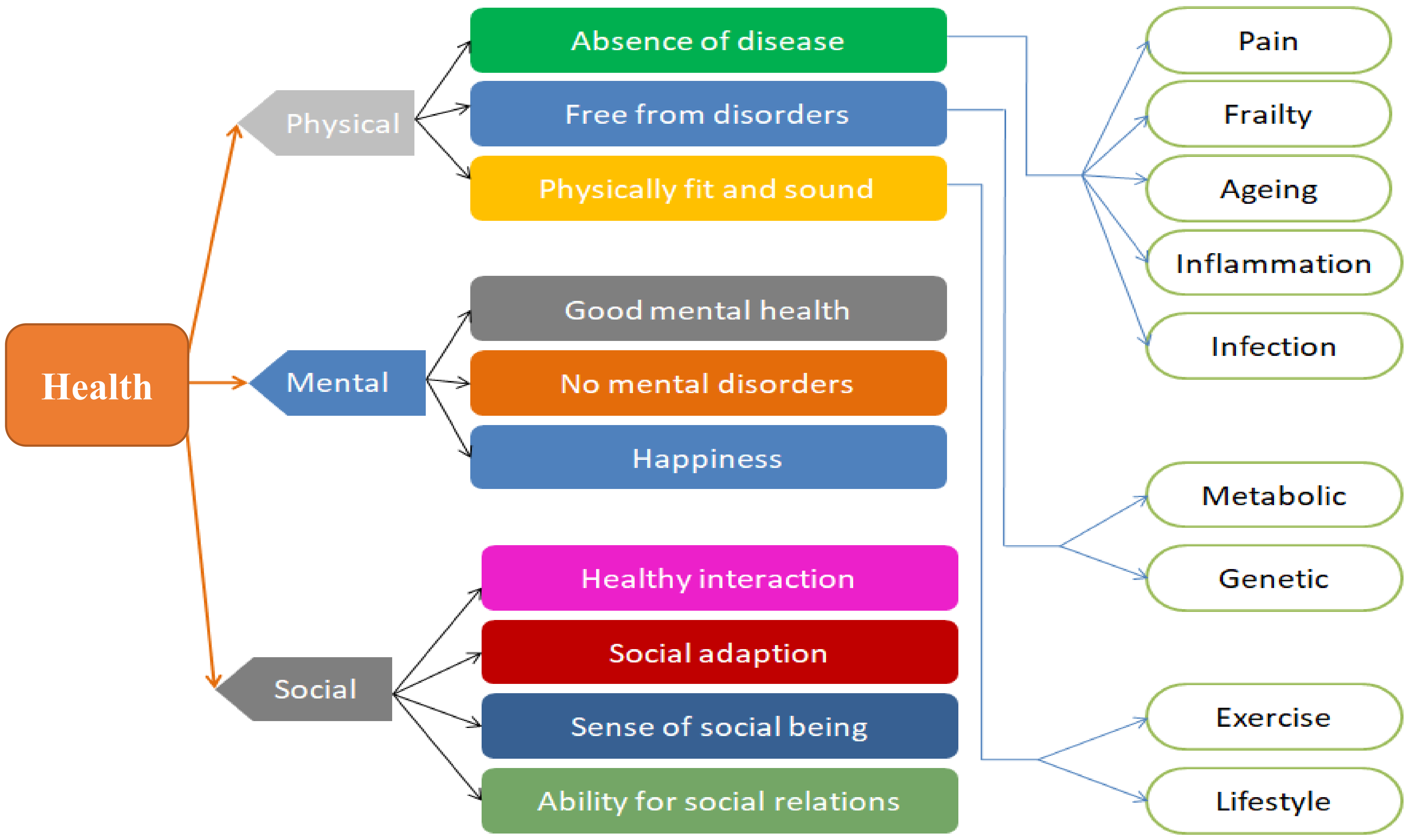
3.
   - Geriatric care, Drugs, lifestyle, value based care, prophylactic, palliative and preventing hospitalization and falls.

“Health is a state of complete physical, mental and social (also emotional and spiritual) wellbeing and not merely the absence of disease or infirmity”

Aging can be defined as the time-related deterioration of the physiological functions necessary for survival and fertility.

Immune, kidney, liver and metabolic

Health-Ageing-Disease Relationship



Disease – A Perturbation in Health: A Mathematical Model

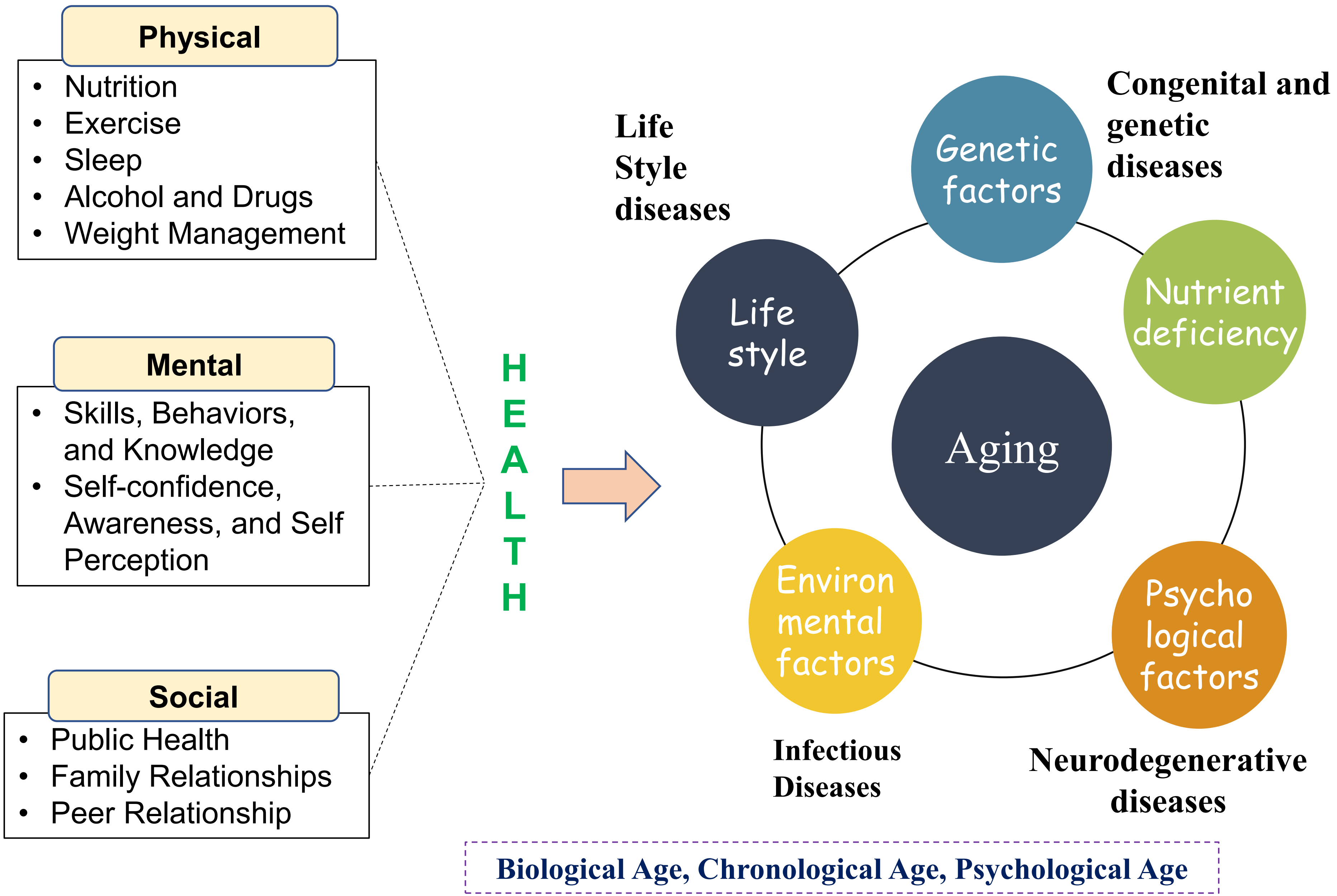
Disease = Health + Perturbation

Health = PW + MW + SW

PW = Physical well-being
MW = Mental well-being
SW = Social well-being

Disease ≠ Sickness ≠ Illness ≠ Malady

Data driven, structural biology and molecular modeling
Unraveling the pathophysiology of degenerative diseases and disease progression



Major Dimensions

- Aging, biological age, psychological age
- Circadian rhythms, sleep, biological clocks, stress
- Nutrition, work life balance, Stress at work, home, and in the society at large
- Emotional and Social
- Spiritual: Enthusiasm to work, passion to perform, desire to excel, enjoy the Life

Aging research (at IITH)

- We are keen to develop metrics for biological, psychological, functional and emotional aging
- One key area is how different organs age differently in humans
- What we can learn from other organisms
- Circadian rhythms, nutrition, lifestyle and diseases

ANOTHER KEY AREA is PAIN

Frailty

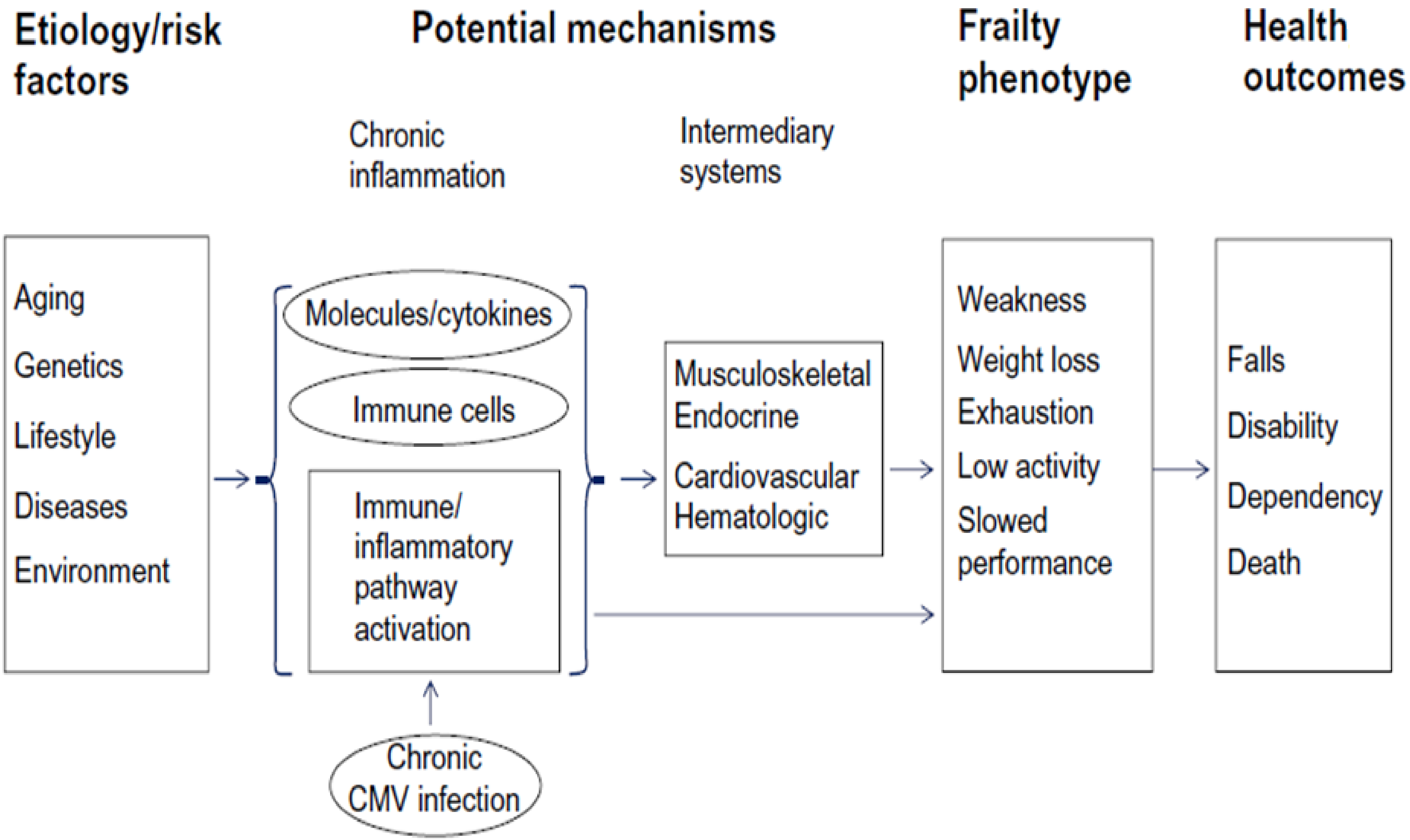
Frailty - characterized by decline in physiologic reserve and function across multi-organ systems, leading to increased vulnerability for adverse health outcomes.

Frailty phenotype criteria (3 or more/5)

- Unintentional weight loss
- Weakness
- Exhaustion
- Slowed walking speed
- Low level of physical activity

"Health is a complete physical, mental and social wellbeing and not merely the absence of disease or infirmity"-WHO

Pathogenesis of frailty syndrome



Stress at Work Place

- Demands of work and ability to cope up.
- This is highly specific to an individual.
- Developing a generic cause and effect theory have fundamental limitations.
- Physical, emotional, and social factors and may not correlate linearly with the job performance.

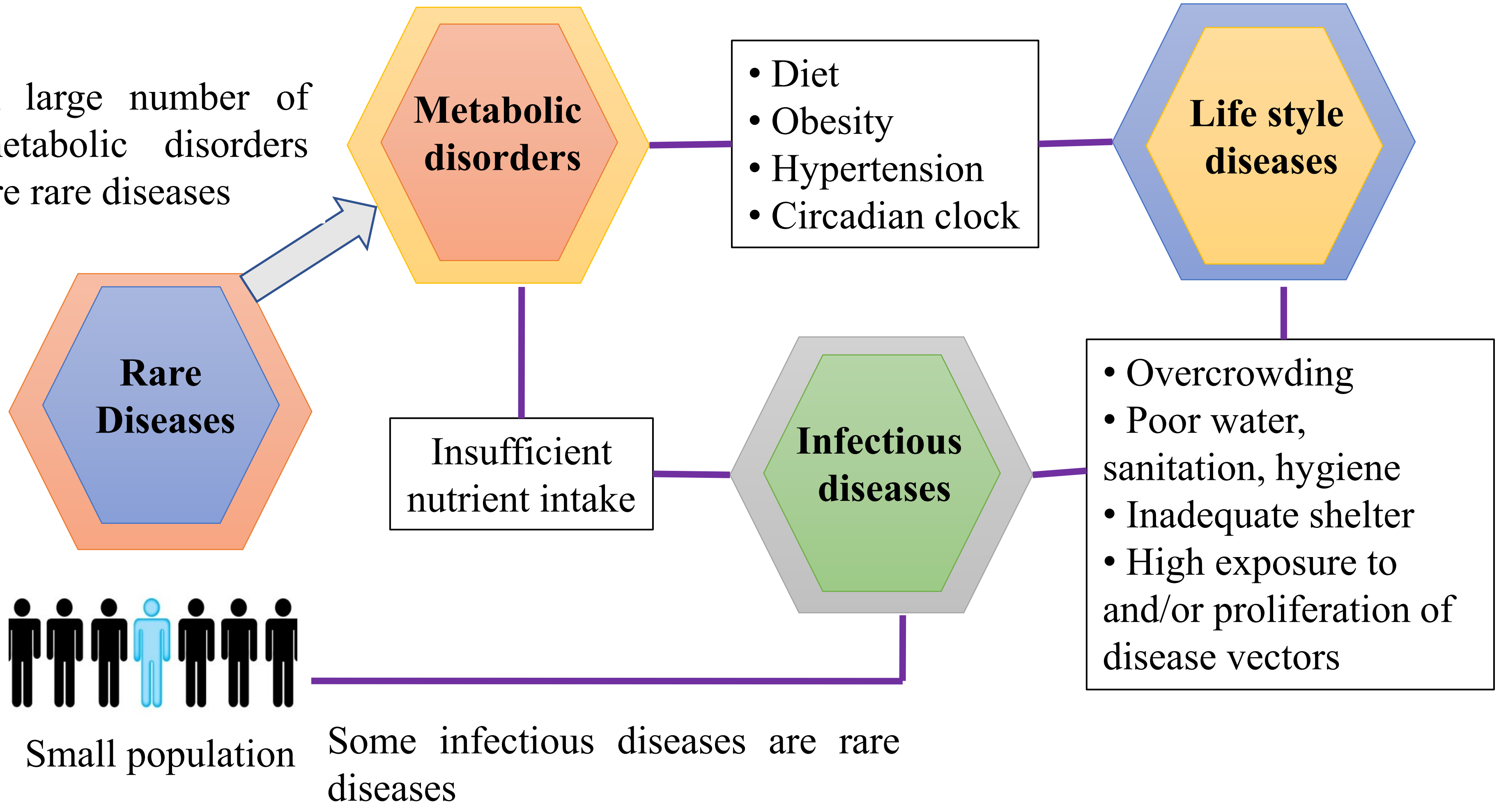
Causes of stress at workplace

- Physical: demanding deadlines, ambiguous goals, deficiency in judging skills/abilities

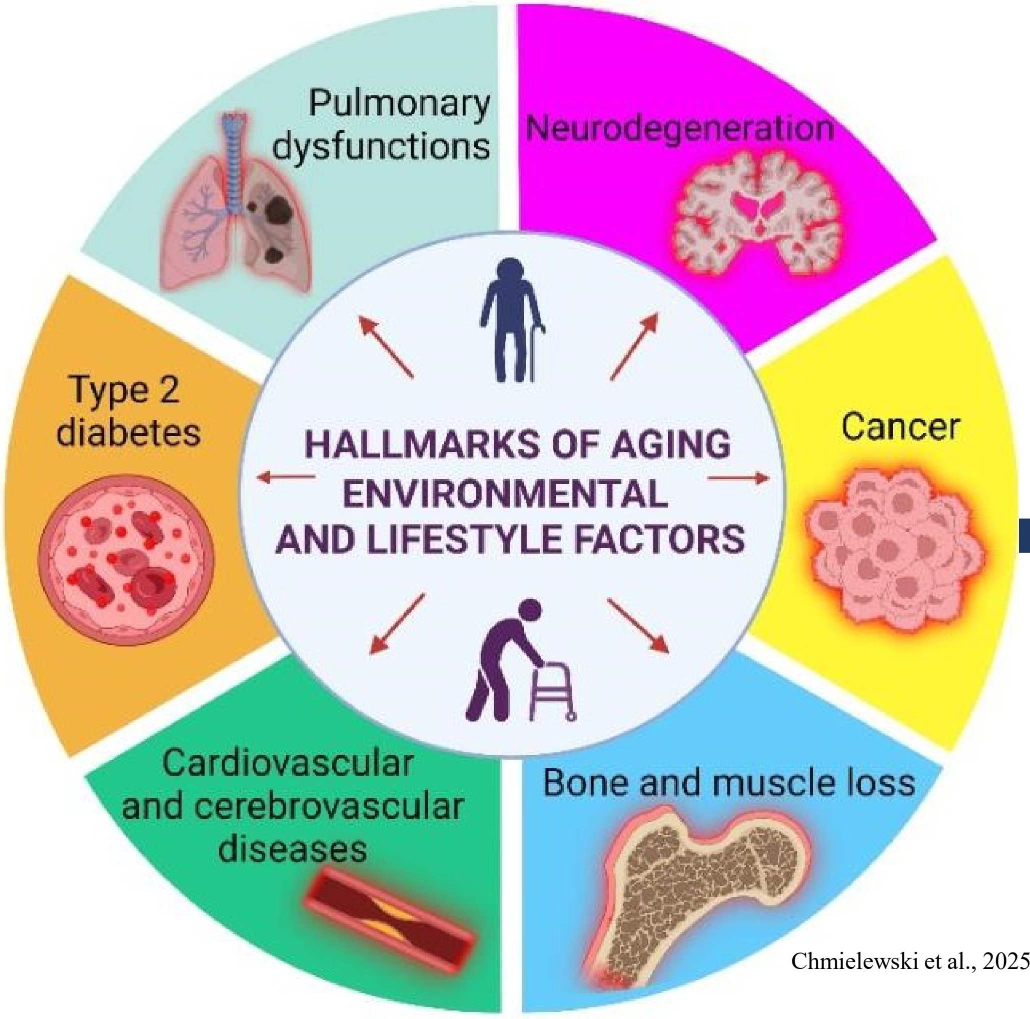
- Mental: poor management, difficult relationships. confusion and anxiety, lack of support/control, bullying and conflict of interest.

- Society: job insecurity, financial, conflicts, personal issues, health of individual or family members.

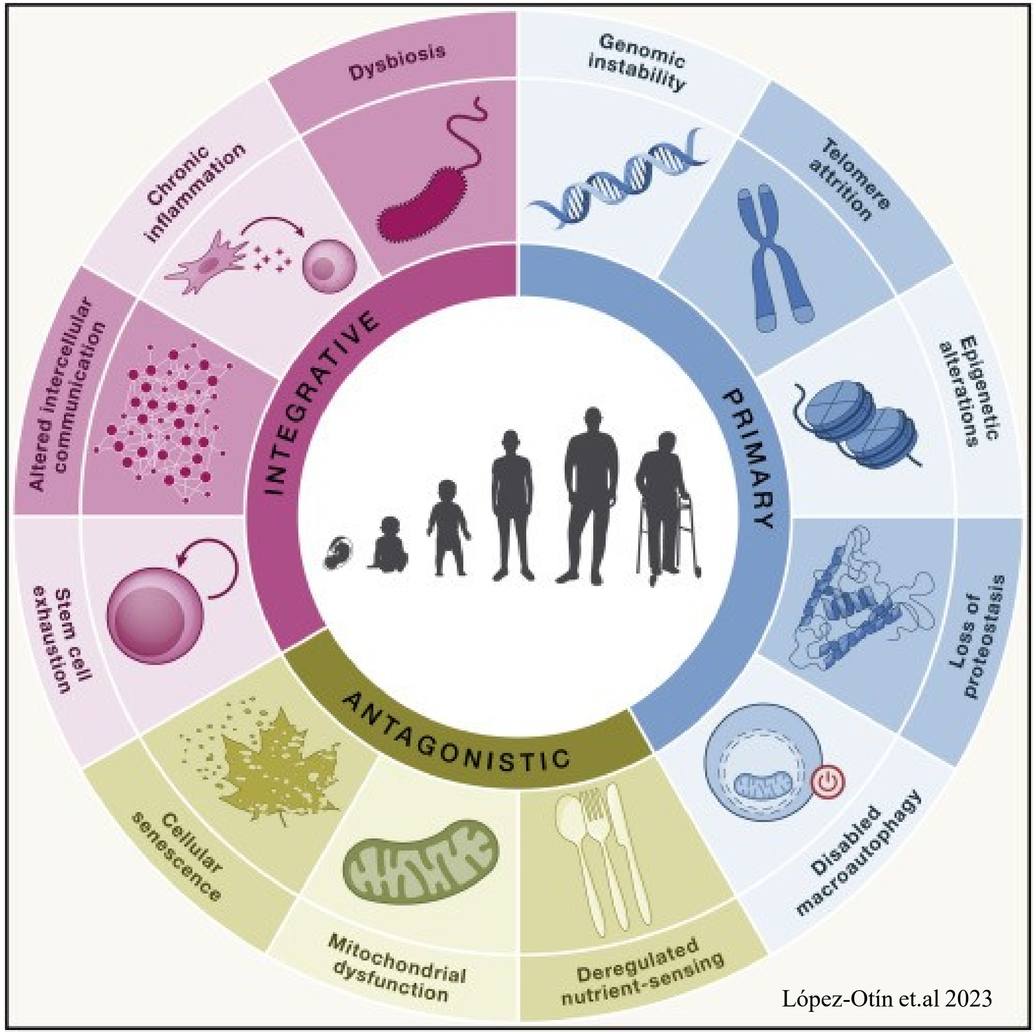
Factors Connecting Rare Diseases, Metabolic Disorders, Lifestyle Diseases, And Infectious Diseases



Hallmarks of Aging and effects



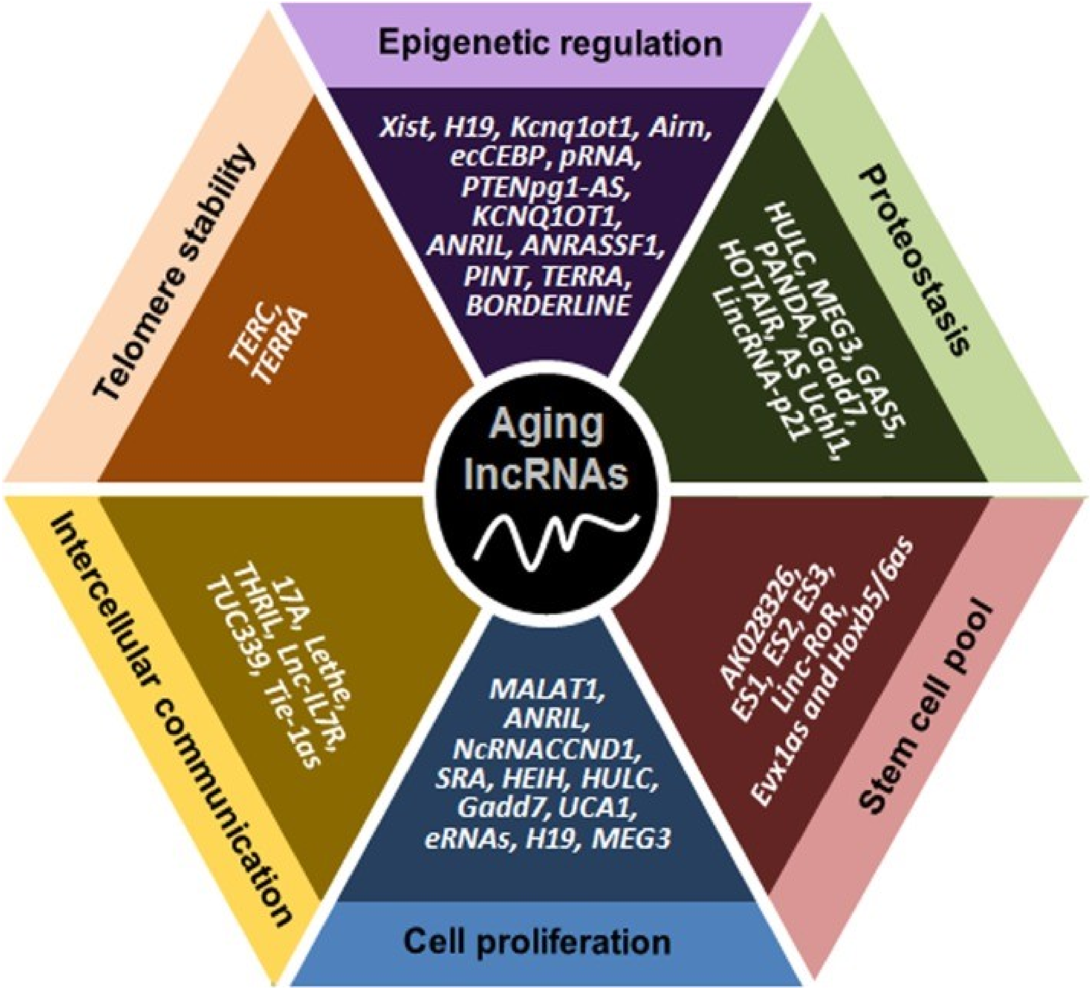
Chmielewski et al., 2025



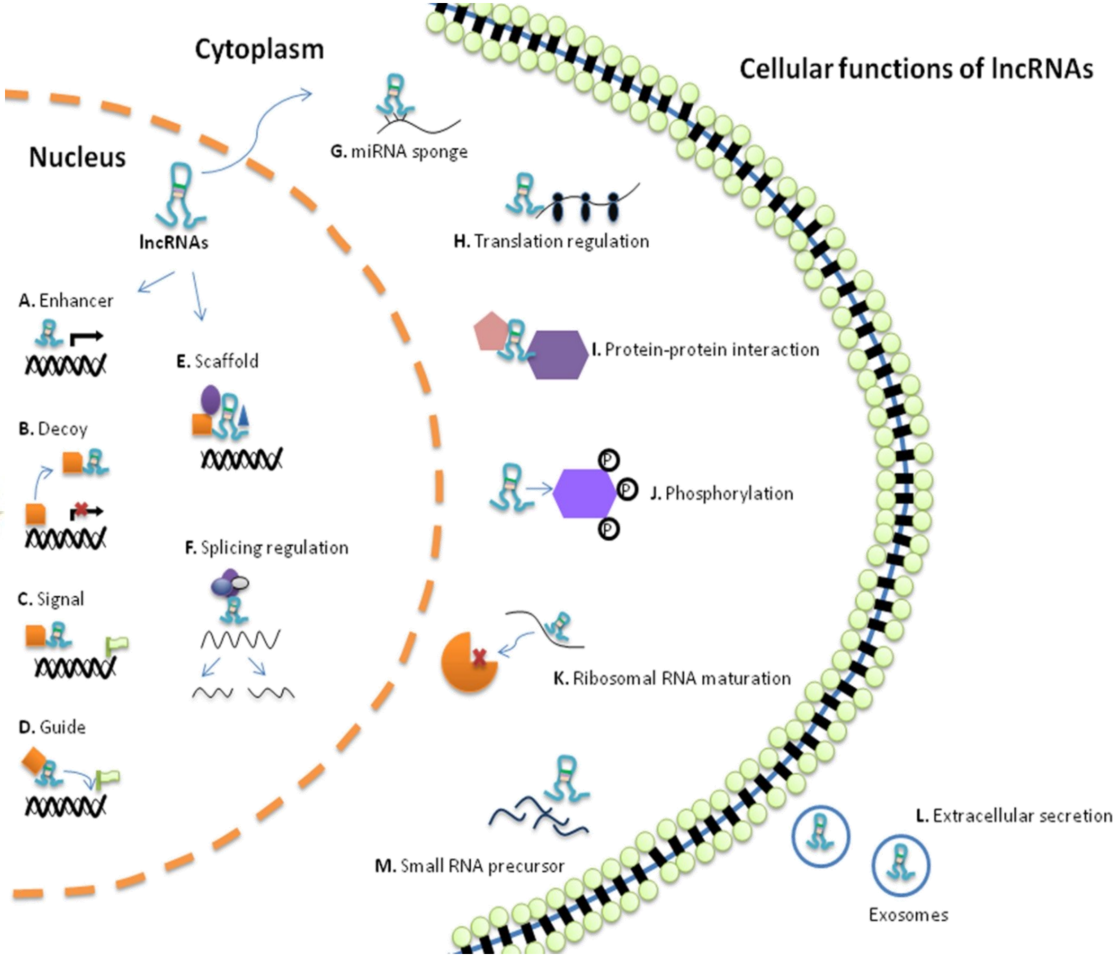
López-Otín et.al 2023

- Chmielewski et al., (2025). Aging and Disease, 16(4), 1853–1877.
- López-Otín et al., (2023). Hallmarks of aging: An expanding universe. *Cell, 186*(2), 243–278.

Role of lncRNAs in Aging



Grammatikakis et.al 2014

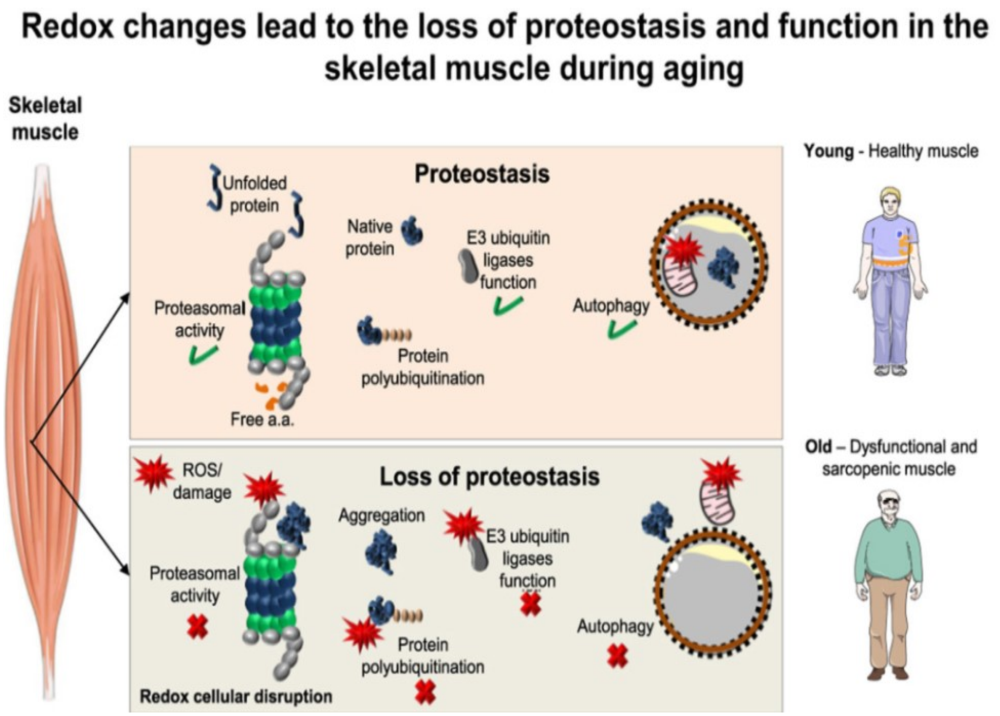


He.et.al 2018

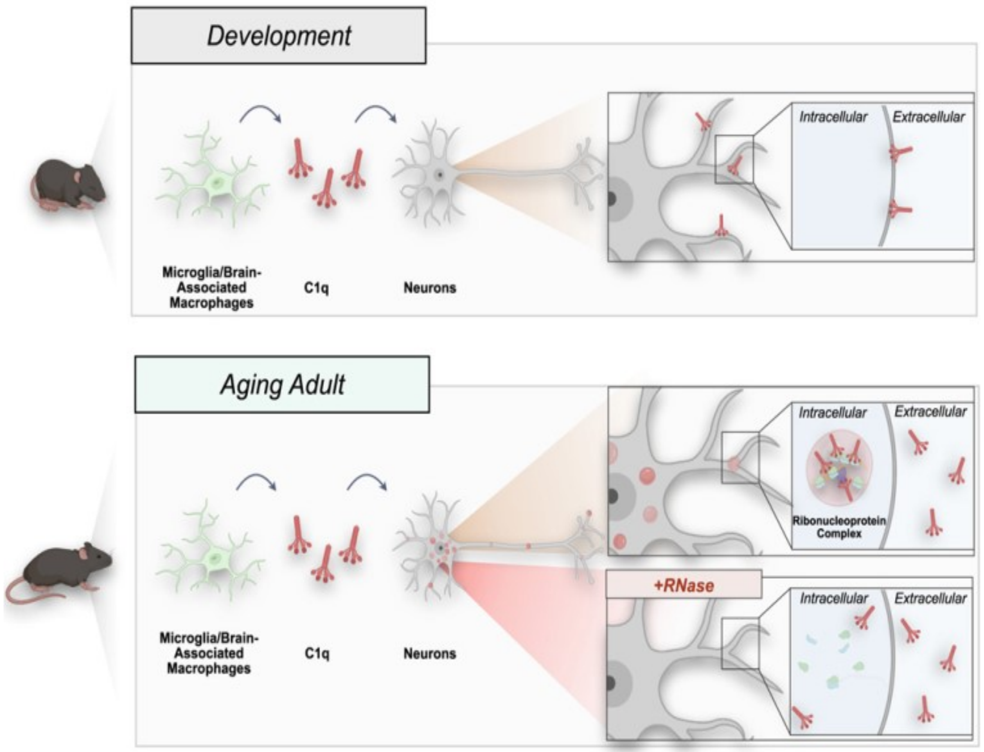
- Grammatikakis et al., (2014). Aging (Albany NY), 6(12), 992–1009.
- He et al., (2018). Aging Medicine (Milton), 1(2), 158–175.

Proteostasis and Aging

- Previous research has demonstrated a strong correlation between protein function and the aging process. (Fernando et.al 2019; Hewitt et.al 2024).



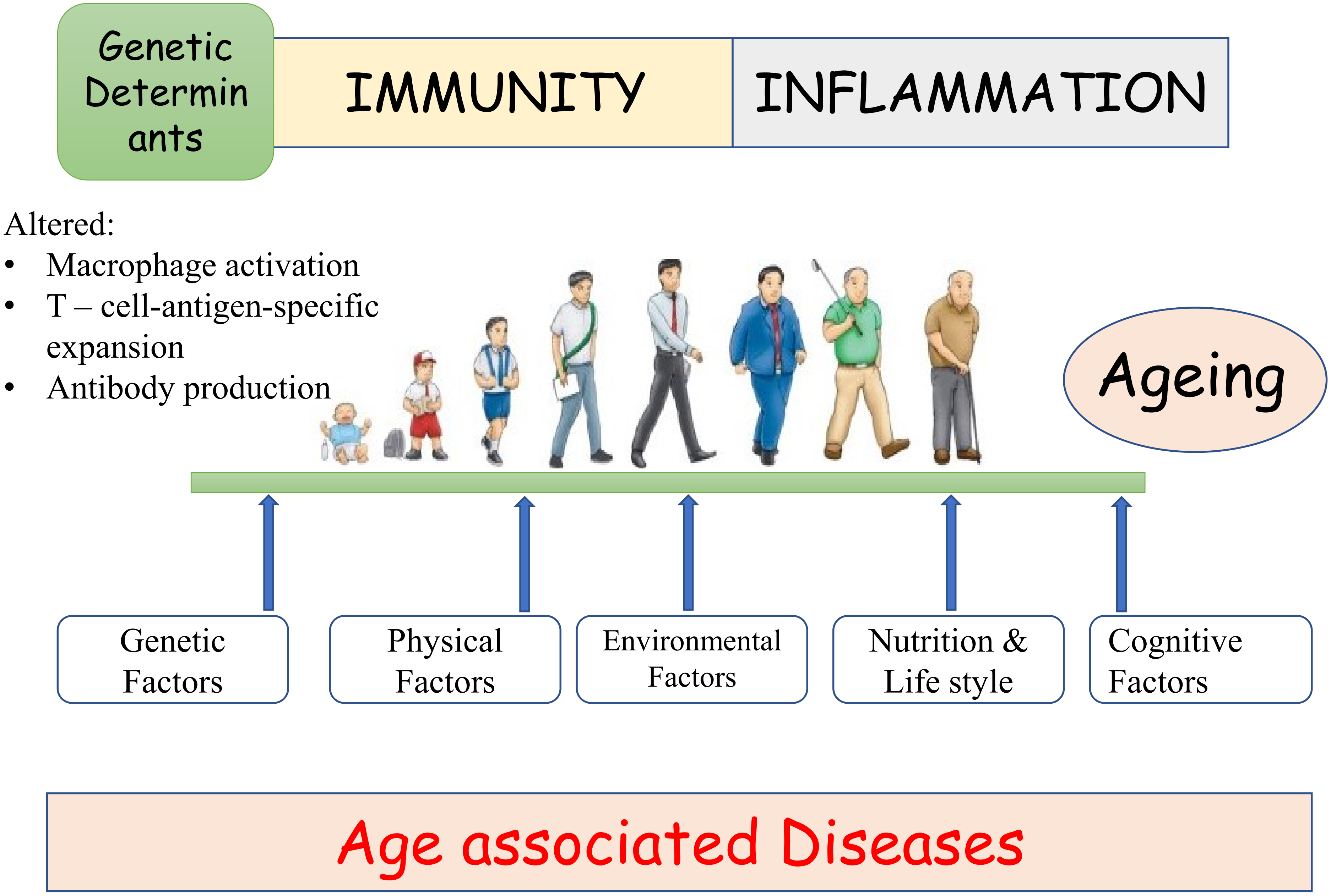
Fernando et.al 2019



Hewit et.al 24

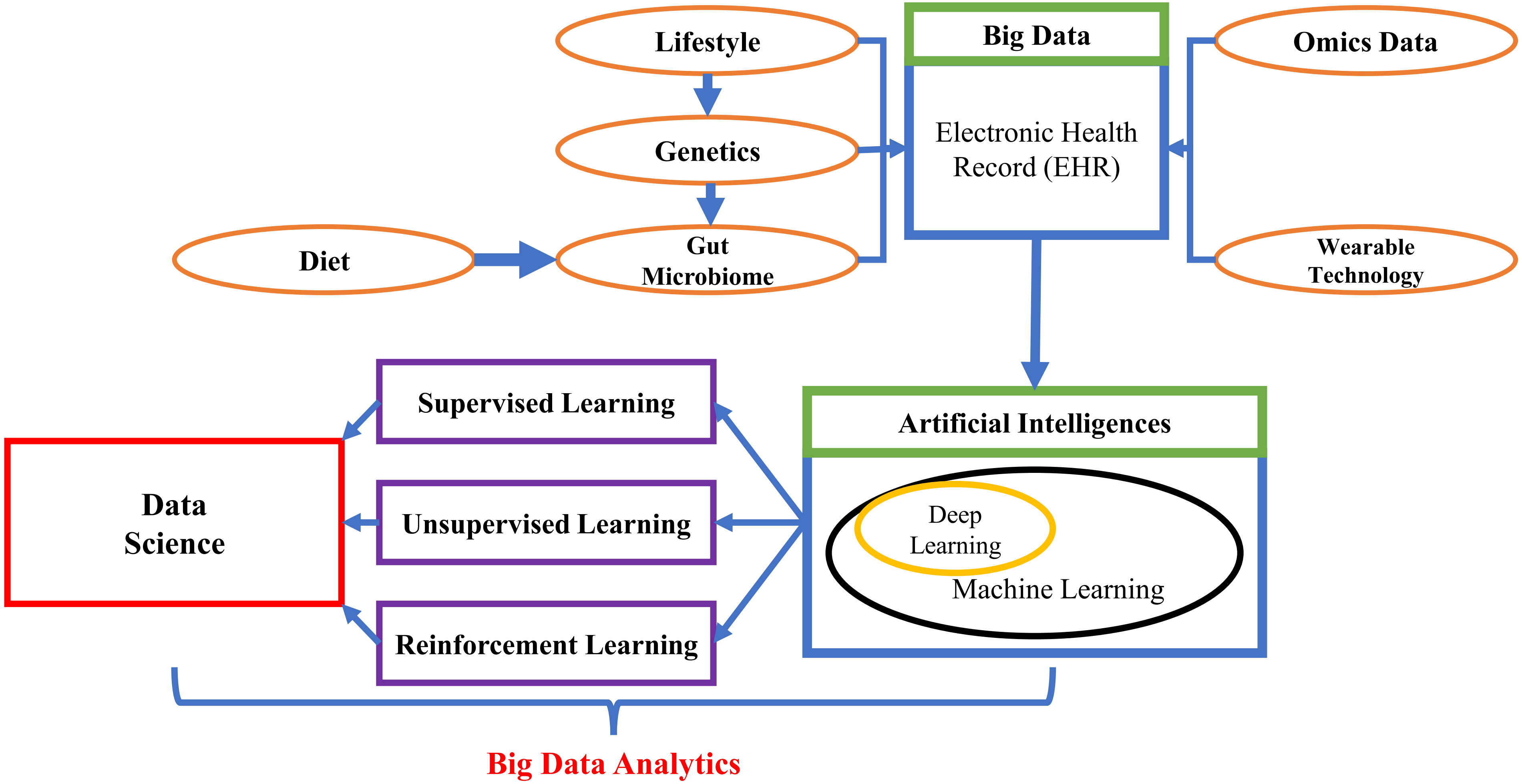
- Although ~20,000 proteins have been identified in humans, only a few hundred to over a thousand of them have been classified as aging-related (Nature Metabolism, 2025) .

- Fernando et al., (2019). Free Radical Biology and Medicine, 132, 155–160.
- Scott-Hewitt et al., (2024). Cell, 187(16), 4193–4212.e24.
- *Nature Metabolism, 7*(1), 14–15.

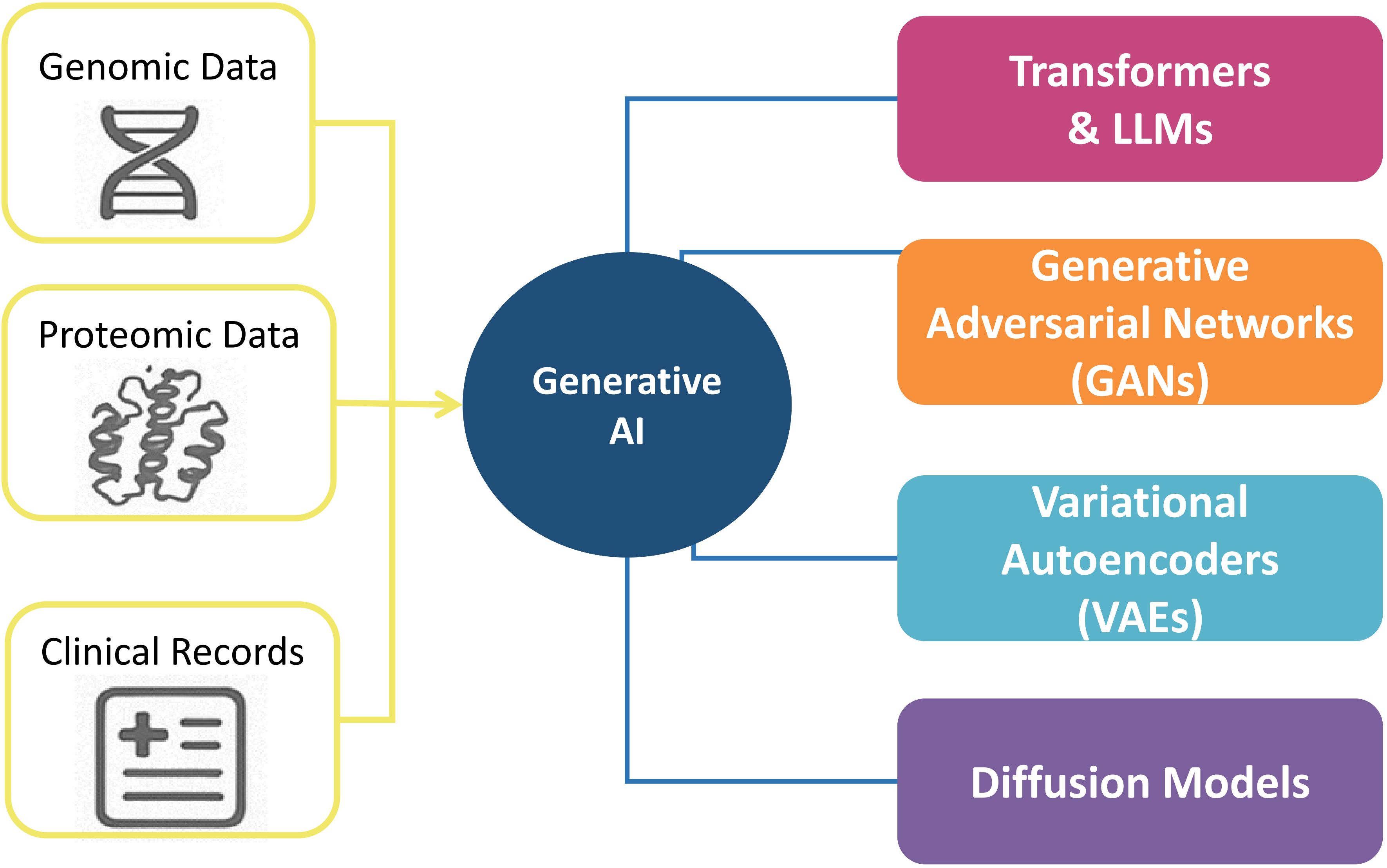


Genetic Determin ants
IMMUNITY
INFLAMMATION
Altered:
• Macrophage activation
• T – cell-antigen-specific expansion
• Antibody production
Ageing
Genetic Factors
Physical Factors
Environmental Factors
Nutrition & Life style
Cognitive Factors
Age associated Diseases

Precision Medicine
P4 (predictive, preventive, personalized, participatory) medicine



Generative AI in Biological Aging

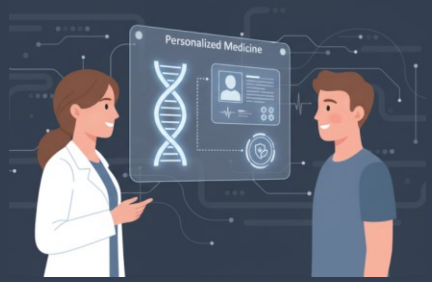


Applications

- Multimodal aging clocks [1]
- Literature analysis
- Novel therapeutic target discovery [1]
- Biomarker discovery
- Chronological age estimation from noisy inputs [2]
- Simulating molecular aging [3]

Agentic AI and Gen AI Emerge as Great Players

Personalized Medicine



Acts as an adaptive health manager, autonomously tailoring treatments and therapies to an individual's evolving biological profile.

Metabolic Disorder

Operates as a real-time optimizer, integrating lifestyle, omics, and clinical data to manage and prevent metabolic dysfunctions.

Aging

Functions as a longevity explorer, discovering and optimizing interventions that slow biological aging and age-related decline.

Chemical and Biological Space

Serves as an autonomous scientist, navigating vast molecular and biological landscapes to design novel compounds, proteins, and therapeutic strategies.

Personalized Medicine and Nutrition

Traditionally, treatments and diets were standardized. But humans are biologically unique. Generative AI helps move from population-level averages to individualized care plans

Applications

01

Drug Discovery & Repurposing:
Generative models (e.g., AlphaFold, diffusion-based drug design) create novel molecules tailored to a patient's genetic profile.

02

Personalized Nutrition:
AI analyzes *genomics, metabolomics, microbiome profiles,* and lifestyle data. It can then generate custom diets—balancing macronutrients, suggesting supplements, and even simulating how a specific food impacts *your* gut bacteria and long-term health

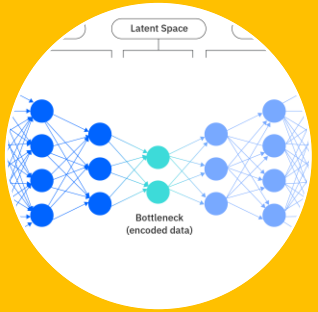
03

Digital Twins for Health:
Generative AI creates a virtual twin of your body to simulate drug responses or nutritional interventions before they are tried in real life.

04

predictive Preventive Medicine:
Instead of waiting for disease, AI forecasts risks (diabetes, cardiovascular, cancer predispositions) and designs tailored lifestyle strategies.

Key techniques:



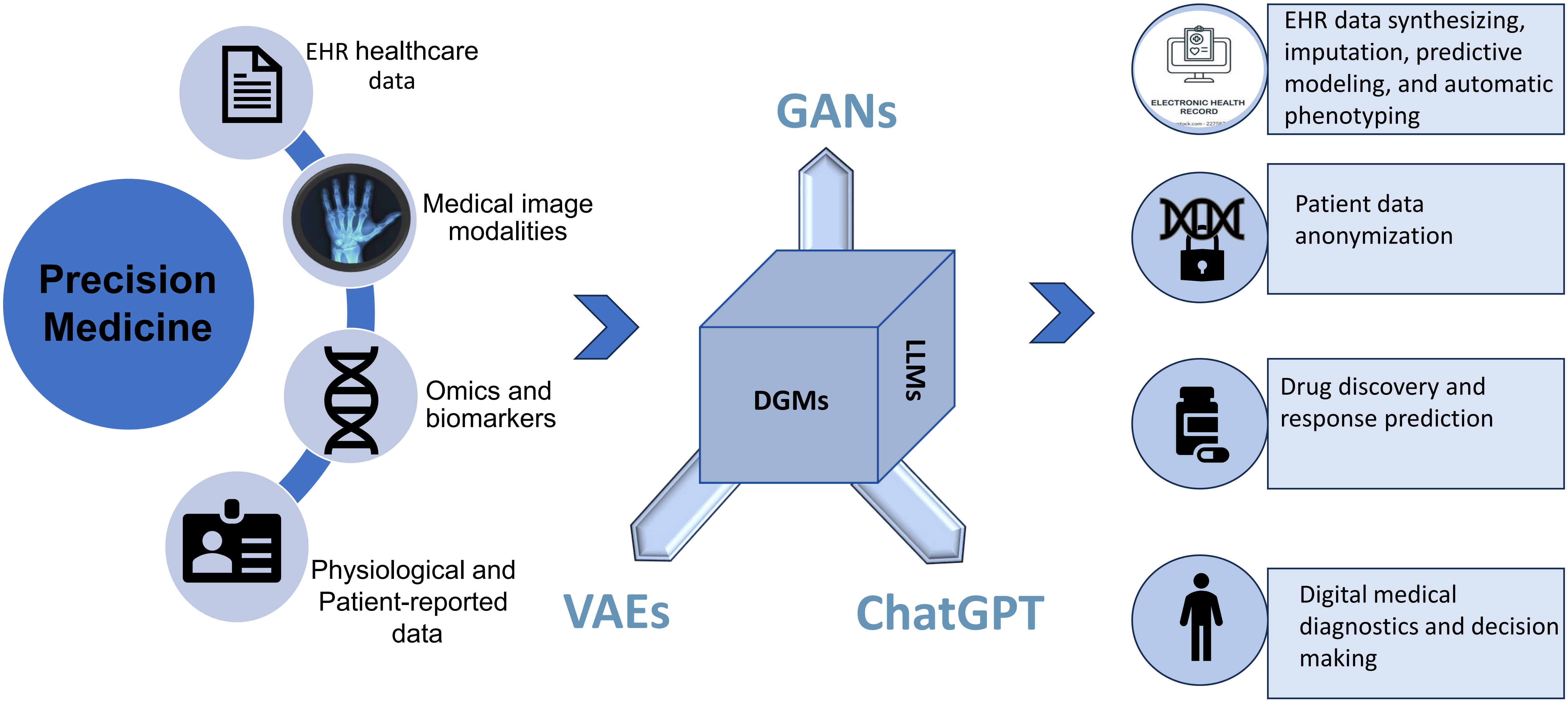
Variational Autoencoders (VAEs): Encode data into a lower-dimensional latent space, allowing **probabilistic reconstructions** and **interpolations**.

Generative Adversarial Networks (GANs): Train a generator to produce realistic fake data, while a discriminator tries to detect fakes — leading to highly **realistic simulations**.

Diffusion Models: Reverse the noise-adding process to learn how to generate clean samples step-by-step from noise — used for **denoising and data augmentation**.

Transformers (e.g., scGPT): Model sequences of gene expressions across cells to capture **contextual and temporal relationships**.

Personalized Medicine



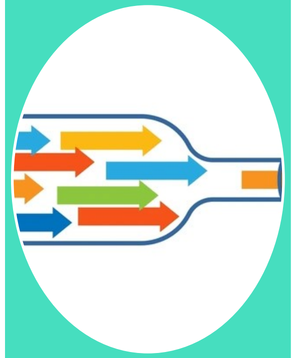
Why do diseases manifest differently in individuals : Going to the core issue

*Despite massive advances in data collection and diagnostics, we still grapple with understanding **why and how individuals differ in their disease progression, drug response, and therapeutic outcomes**.*

Diseases like cancer, Alzheimer's, autoimmune disorders exhibit extreme variability between individuals.

Treatment responses vary widely; some patients respond remarkably, while others worsen — often with no clear reason.

Most therapies still follow a one-size-fits-all model, rooted in population averages rather than personalized biology.



The core bottleneck in many of these failures is our limited understanding of intra-tissue, intra-patient variability — what we now define as cellular heterogeneity.

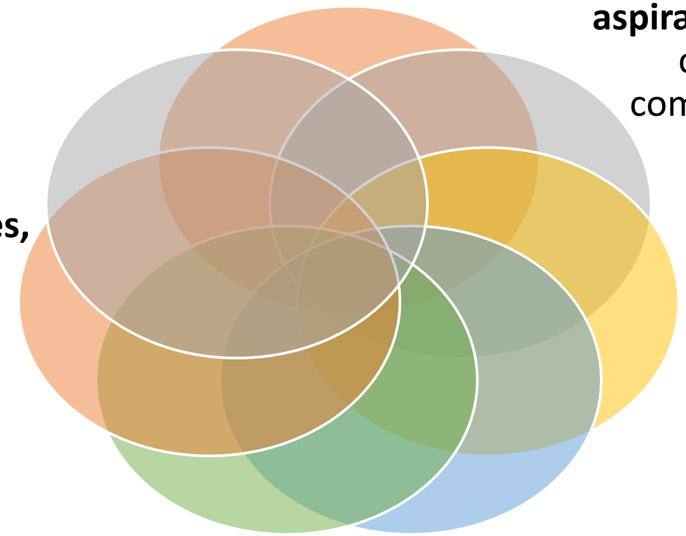
We must now shift from "disease labeling" to continuous modeling of cellular states — where cell identity, function, and transitions are not binary, but dynamic and nuanced.

The Grand Challenge of Healthcare in the 21st Century

Healthcare today is at a crossroads: the data we collect is enormous, yet our understanding often remains superficial.

Underlying problem: **we're treating averages, not individuals**.

Rising burden of **chronic, multifactorial diseases**: cancer, neurodegeneration, autoimmune disorders.



Precision medicine remains **aspirational** because the tools to characterize biological complexity are still evolving.

One-size-fits-all therapies fail to account for individual biological variation.

Patients respond **differently** to the same drug, with unknown causes.

Clinical trial failures are common due to lack of predictive biomarkers.

Cellular Heterogeneity

*Cellular heterogeneity refers to the **diversity of cell types, states, and responses** within the same tissue or disease microenvironment. It's not noise — it's **biological reality**.*

Every tissue, from the brain to the tumour microenvironment, is a mosaic:

- Cells vary in their transcriptional, epigenetic, proteomic, and metabolic states.
- Even cells that appear morphologically similar can have different functional identities and fate trajectories.

In health:

- Cellular heterogeneity enables adaptability, plasticity, and resilience.

In disease:

- Heterogeneity causes drug resistance, relapse, and failure of diagnostics.
- A tumour with a subpopulation of drug-resistant cells can survive therapy and regrow.

Therefore, understanding cellular heterogeneity is not just important — it's foundational for next-generation precision medicine.

Data Deluge! Noise vs Signal

Biological data is expanding exponentially, but our analytical methods haven't kept up. ***More data ≠ more knowledge****, unless we can interpret and model it effectively.*

Single-cell experiments generate **gigabytes per sample**, often covering **hundreds of thousands of cells**.

These datasets are:

- **High-dimensional** (20,000+ genes per cell).
- **Sparse** (many genes not expressed per cell).
- **Noisy**, with both biological and technical variation.

Standard methods (clustering, PCA, t-SNE) flatten complexity:

- They can **visualize data**, but they don't **model transitions, fates, or responses**.
- **Labels are hard to define**, making supervised learning difficult.

What's needed:

- **Unsupervised**, **flexible**, and **probabilistic** models that can learn from noisy, incomplete data and simulate new biological possibilities.

Generative AI — A Paradigm Shift in Biological Modelling:

Generative AI models don't just describe data — they ***learn the rules*** *behind it and can* ***generate new, plausible samples****, simulate perturbations, and infer hidden structure.*

Generative AI focuses on **learning probability distributions** of data:

- From this learned representation, it can **generate new examples**, **fill in missing parts**, or **simulate alternate outcomes**.

It is fundamentally **different from traditional ML**:

- It is **not just predictive**, but **creative** and **simulative**.

Modeling Cellular Heterogeneity with Generative AI:

Traditional methods either collapse heterogeneity or ignore rare populations.

traditional methods tend to **average out** the differences among individual cells or samples. For example, in **bulk RNA sequencing**, the expression levels are measured across millions of cells together — and the result is an **average**.

Generative models can:

- Learn **low-dimensional embeddings** that represent **continuous cellular states** (e.g., cell cycle, differentiation).
- Distinguish between **true biology and noise**.
- Reconstruct **intermediate or missing states** along a differentiation or disease progression pathway.
- Identify **latent disease programs** that might not be obvious in static data.

By using **conditional latent spaces**, we can simulate:

- What happens when a gene is knocked out.
- How cells will respond to immunotherapy.
- Which patient cells might develop resistance.

Trajectory Inference + Generative Modeling = Predictive Disease Maps

Understanding how cells change over time is essential. With generative models, we can move from snapshots to ***biological movies***.

Trajectory Inference (TI) methods reconstruct cellular progressions (e.g., from stem cells to differentiated cells, or from healthy to cancerous states).

Limitations of traditional TI:

- Static graphs, no simulation.
- Assumptions about branch points.

Generative AI adds:

- Stochastic simulations of future cell states.
- Ability to simulate divergent paths, perturbations, or reversions.
- Inference of probabilistic fate landscapes.

This means we can:

- Predict which cells will transform in cancer.
- Model immune exhaustion or rejuvenation.
- Simulate response and relapse trajectories under therapy.

Some Thoughts –Generative Biology: Implications on disease, health, evolution, and aging !

Cellular heterogeneity is not a nuisance — it’s the key to decoding biology.

Generative AI allows us to embrace that complexity, not run from it.

When biology becomes generative, we will be able to:

- Understand disease in real-time.
- Simulate health interventions.
- Design better experiments and treatments.

This is not just AI for biology — it is the future of biology itself.

Geriatric Care

- It’s a big area, with many opportunities in improving the quality of life of humans, decreasing the financial burden as well as improving the economy of the country.

- We are involved in the Geriatric care through AI (value-based care, prophylactic, curative, palliative, personalized and preventive (especially falls and hospitalization) and treating the end-terminal patients.

Aging, personalized, and geriatric care

- The role of AI, (Gen-AI, agentic, robotics) are going to play a significant role and are going to replace some of the thing exclusively done by humans.

- Research ideas, fundamental advances in new knowledge and cellular heterogeneity

- Data Generation and Analytics

An interesting/disturbing scenario !

- Man/Animal
- Man/Machine
- Man/Technology
- Creativity, imagination, thinking, feeling, understanding, care, empathy, originality, novelty, and wisdom appear to be hallmarks of humans…..

……………….Is it so??!!

Acknowledgment: My funding agencies: CSIR, DST, DBT, IITH, MEITY, AICTE, Several Industries
All my students and collaborators. IIT Hyderabad for giving us a chance to excel.

Fifth Paradigm Lab , IIT Hyderabad

Pratiksha, Kalyani, Vandan, are missing in photo

Thank You!!