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A SUMMARY OF RESEARCH ON HUMAN AGEING AND LONG LIFE BASED ON PHENOMIC AND GENOMIC DATA

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Abstract
Human ageing is a deeply individual process that progresses throughout life and results in significant variation among people in terms of how their physical abilities, health, and lifespan decline. This variation can be seen clearly when comparing healthy and active centenarians to 60-year-olds who are already dealing with multiple chronic illnesses. Molecular research exploring the reasons behind this diversity uses a wide range of methods and targets. In most of these studies, researchers focus on either how long a person lives or on biological markers that show the rate at which ageing occurs in individuals and their tissues.However, unlike many complex age-related diseases, scientists have not yet agreed on a standard set of biomarkers or phenotype definitions that can be used in genetic or genomic research on ageing and lifespan. Similar to what is found in animal studies, common biological features associated with disease risk, healthy ageing, and longevity include immune system and metabolic pathways.Many genomic and epigenomic studies have discovered potentially important genes and biological pathways linked to ageing and lifespan,

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with APOE and FOXO3A being the most consistently confirmed genetic markers. Research is still ongoing to understand the function of certain genes using cell and animal models. The future of ageing and longevity research depends on better interpretation of genomic data, using computational and systems biology tools, integrating findings from animal models, and ensuring consistency in collecting phenotypic and omics data across long-term and experimental studies.This article is part of a special collection titled Model Systems of Aging, edited by Houtkooper Riekelt.

Keywords: Human Ageing, Phenotypic markers, Functional decline, Dementia, Mendelian diseases, Biological ageing, Epigenetic changes, Biomarkers, Serum proteins and metabolites.

Introduction

1.Phenotypes and endpoints of human ageing. As humans age, changes happen at the molecular, cellular, and anatomical levels across all body systems. However, it's often unclear which of these changes should be used as phenotypic markers to study their genetic or molecular causes. A key question is whether these physical changes represent the early stages of functional decline that eventually lead to disease.For instance, there is still ongoing debate about whether plaques and tangles found in the ageing brain are early signs of dementia or part of another process. It's also uncertain whether diseases that begin early in life and those that appear later share similar causes. Although some genes involved in Mendelian diseases—like early-onset osteoarthritis or dementia—show ageing-like features, they may not fully explain the slow degeneration and functional decline seen in older adults, which raises their risk of illness and death.In ageing research, it is important to study traits across the entire human lifespan. Early life factors—such as birth weight, childhood body composition, and bone growth—are linked to later health conditions like cardiovascular disease and osteoarthritis. Similarly, traits from mid-life, such as poor physical strength, are associated with higher mortality risks in old age.Molecular studies often accompany these observations, especially at the phenotypic level. For example, long-lasting epigenetic changes in the genome, caused by early life stress such as the Dutch Hunger Winter, are linked to health problems later in life.Because of this, research into the biology of ageing looks at a wide variety of age-related traits throughout life. These include changes in function—like memory, grip strength, walking speed, balance, lung function, heart rate, and general well-being, measured by physical tests or questionnaires.Researchers also use health indicators like blood pressure, cholesterol, insulin resistance, and bone density as markers of ageing. Epidemiological and clinical studies explore how often people get age-related diseases—like dementia, diabetes, or stroke—and the biomarkers that go with them. In addition to studying ageing traits, researchers also examine lifespan outcomes, such as total lifespan, cause-specific death, and how long people live without disease. Inspired by animal research, human studies on longevity often define it as living beyond a certain age limit.

2.Biomarkers. Ageing is a very personal experience and is influenced only partly by genetics. Even animals with the same genetic background and identical diets often show large differences

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in how quickly they age and when they die. Because of this, much of human ageing research focuses on finding biomarkers that can measure how fast someone is biologically ageing, rather than just looking at their chronological (calendar) age.These biological markers could help predict future health outcomes and allow doctors and researchers to track whether medical treatments or lifestyle changes are actually slowing down ageing and improving health. There are several types of biomarkers used to assess the ageing process. These include:

-Serum proteins and metabolites

-Genetic markers like somatic mutations and telomere length

-Epigenetic changes, such as DNA methylation and RNA molecules (messenger RNA and microRNA)

-Physical function tests, like memory checks and handgrip strength

Some individual biomarkers used in clinical research include serum glucose levels, fT3 hormone levels, CDKN2A (p16) gene expression, and leukocyte telomere length (LTL). LTL, in particular, has been widely studied for its link to various health outcomes, including risk of death.In other cases, researchers use tissue-specific biomarkers to study certain diseases—for example, urine-based markers that show bone or cartilage breakdown, which are useful in osteoporosis and osteoarthritis studies.More reliable than single indicators are multi-biomarker models, which combine several measures to estimate biological age. Some examples include:

-The original Frailty Index

-The Frailty Index

-The NHANES-based 10-biomarker model of “Biological Age”

-A model designed for younger adults (under 40) that considers changes in multiple organs like the lungs, heart, liver, kidneys, and immune systemThese complex tools often do a better job than chronological age at predicting someone’s risk of death or decline in physical ability over time.In the rest of this work, we will look at the latest developments in omics-based biomarkers—which include data from the genome, epigenome, transcriptome, and metabolome—to better understand biological ageing.

3. Omics biomarkers. In recent years, omics technologies (such as transcriptomics, epigenomics, metabolomics, and proteomics) have significantly contributed to the identification of biological age markers. Initial studies focused on candidate gene expression and methylation in smaller groups, but were later expanded to large cohort analyses, typically using peripheral blood samples collected at one time. Age-related alterations in the transcriptome and DNA methylome have been found to correlate with various health indicators. Several genes identified through blood transcriptome studies were further investigated in animal models, leading to increased attention on pathways like the kynurenine pathway. This article will focus primarily on the advancements in understanding epigenetic and metabolomic changes, which are recognized as key indicators of aging across different species.

3.1. Epigenetic markers. Epigenetic changes, which involve the regulation of gene expression through DNA methylation, chromatin modification, and non-coding RNAs, occur in both the nuclear and mitochondrial genomes as individuals age. Genome-wide studies of DNA methylation

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in peripheral blood have revealed global hypomethylation and gene-specific hypermethylation with age, although these changes typically show a weak correlation with gene expression. Despite this, DNA methylation at many genomic sites correlates strongly with chronological age, leading to the development of biological age predictors based on these methylation-age relationships. One such study calculated the DNA methylation age (DNAmAge) of biological samples from various tissues using the average methylation levels at 353 CpG sites. DNAmAge acceleration, determined by comparing this biological age to chronological age, was found to be a significant predictor of health conditions and mortality, independent of age and traditional risk factors. This marker was linked to cognitive function and, in brain tissues, to the rate of neuronal aging and Alzheimer's disease, and was used in genetic studies.Comparing DNAmAge to other molecular predictors, such as transcriptome age and leukocyte telomere length (LTL), DNAmAge was found to be the most reliable molecular predictor of health and mortality so far. However, studies on aging omics have not yet tracked the decline with age over multiple time points across the lifespan, despite the availability of longitudinal cohort data.While candidate and genome-wide DNA methylation studies do not directly explore mechanisms, the observed epigenetic changes with age likely reflect environmental and stochastic influences on gene function. DNA methylation changes at clock loci or other regions that exhibit near-linear methylation changes with age, such as ELOVL2, are not yet understood mechanistically. It is speculated that immune, inflammatory, or apoptotic processes may drive these changes. Large-scale studies of epigenetic divergence with age have, however, identified CpG loci, particularly those in polycomb-repressed regions of the human methylome, that are linked to gene expression changes related to DNA repair, apoptosis, and metabolic pathways.

3.2. Metabolomic markers. Another important area of omics analysis is the study of metabolites in the human metabolome as potential biomarkers for aging and disease. Metabolomics profiles have been shown to predict various diseases, including cardiovascular disease and type 2 diabetes. Blood metabolome analysis using mass spectrometry has also been linked to familial longevity, while urine metabolomics has been used to create a biological age predictor. Additionally, a stepwise regression analysis of 106 tested 1H NMR-based metabolites identified a profile of 4 metabolites that could predict mortality. The metabolome holds great promise as a source of biomarkers, especially because of the ability to provide biochemical insights (particularly through targeted analysis) into the relationships between metabolites and health parameters.

3.3. Genetic markers of ageing and longevity: somatic mutations. In the 1960s, it was proposed that aging results from the accelerated accumulation of somatic DNA mutations, which in turn leads to errors in protein structure, ultimately disrupting key functions involved in maintaining the body. Research investigating the accumulation of somatic mutations over a lifetime, particularly in blood and other tissues, has been conducted in various middle-aged cohorts, patient studies, and among the oldest individuals. The rate of accumulation varies between tissues due to differences in environmental exposure and tissue renewal rates.For instance, Ye et al. studied monozygotic twins aged 40 and 100 and found only a few discordant somatic single base substitutions in the centenarians' genomes. Their study suggested that living for a century did not result in a large

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number of detectable somatic mutations in blood. In a separate study, the whole genome sequences of a 115-year-old Dutch woman's DNA from several tissues were compared, revealing that her blood tissue accumulated approximately 450 somatic mutations over her lifespan. Despite this, these mutations did not appear to shorten her life.Further research from the Leiden Longevity Study (LLS), involving 218 subjects with an average age of 94, and the Rotterdam Study, with 646 subjects aged 80–105, detected somatic mutations in genes linked to hematopoietic malignancies, particularly DNMT3A and TET2. These genes have been associated with the clonal expansion of hematopoietic stem cells. Other large-scale sequencing studies have shown a significant increase in mutation frequencies of these genes with age, starting from middle age onward. Prospective analyses of middle-aged individuals revealed an increased risk of all-cause mortality for carriers of mutations in these genes compared to non-carriers, suggesting that clonal expansion of hematopoietic stem cells makes the elderly more vulnerable to adverse health effects.However, in contrast, centenarians and nonagenarians who carried these mutations did not show signs of compromised survival over an 8- to 10-year period. Somatic mutations in DNMT3A and TET2 are therefore considered quantitative genetic markers of the aging process and clonal expansion. Their predictive power and contribution to health effects in the elderly population are still being explored.

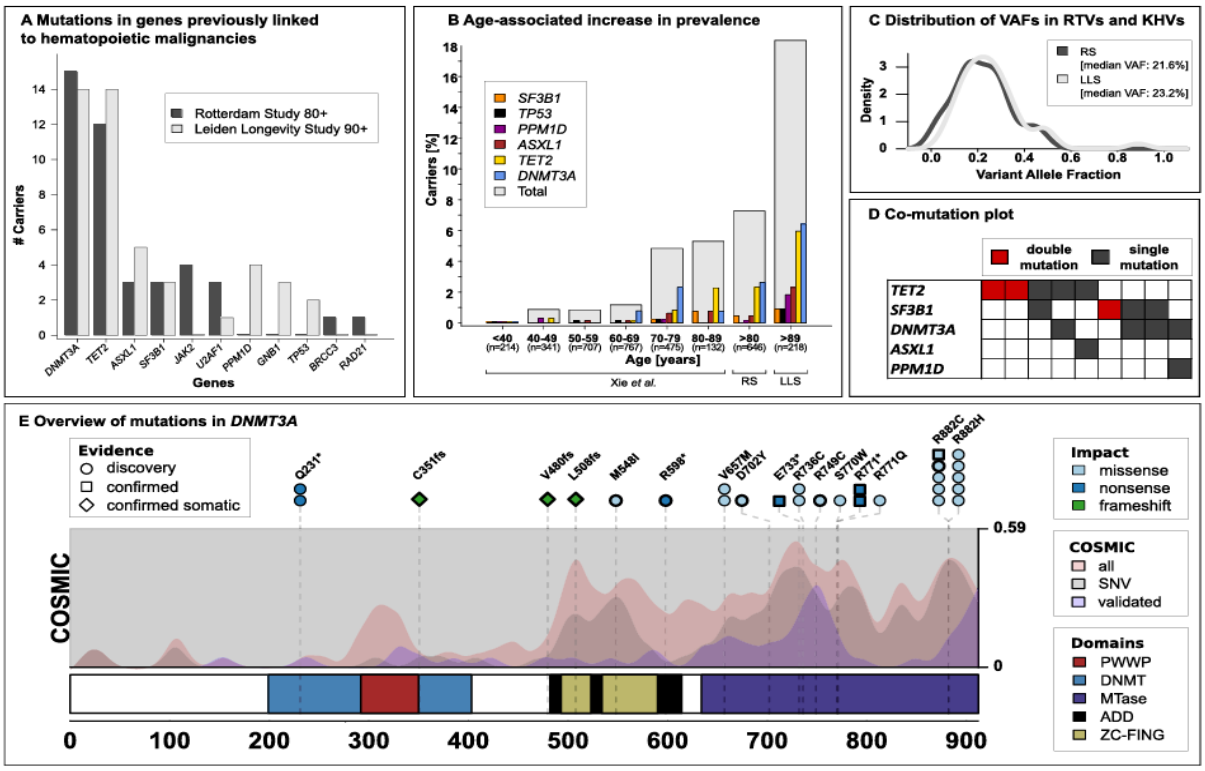

Fig. 1. Age-related increase in the frequency of somatic mutations in blood cancer related genes detected by Next Gen Sequencing in subjects of different age groups.

4. Lifespan and heritability. The human lifespan is significantly influenced by environmental factors, with life expectancy having risen dramatically over the past 200 years. For example, in Western societies, the life expectancy of women increased from 45 years in 1840 to 85 years in 2015. In European countries like the Netherlands, life expectancy for the oldest individuals began

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to rise notably in the second half of the 20th century, with projections indicating the number of people over 65 will double by 2050 and those over 85 will triple. On a global scale, life expectancy has also improved; for instance, children born today in Brazil or Myanmar can expect to live 20 years longer than those born 50 years ago.Some elderly individuals, particularly supercentenarians (those aged 110–119), semi-supercentenarians (aged 105–109), and centenarians (aged 100–104), show exceptional longevity and exhibit little or no signs of age-related diseases. Research has shown that older age groups tend to experience a delay in the onset of major diseases. On average, first-degree relatives of long-lived individuals also enjoy significantly longer, healthier lives compared to those of individuals with average lifespans.Heritability studies, particularly twin studies, have provided insight into the genetic and environmental factors affecting lifespan. These studies suggest that genetic factors contribute up to 27% of lifespan variation in current populations, with the remainder largely explained by environmental factors, such as nutrition, hygiene, and healthcare. The heritability of lifespan tends to increase at older ages, though it remains relatively low overall.Genealogical research in certain families has revealed that lifespan tends to be passed down more frequently from mothers to offspring, especially to daughters. Research into regions with high concentrations of centenarians, often referred to as "Blue Zones," such as Okinawa and Sardinia, has highlighted the role of lifestyle factors in promoting extreme longevity. These regions share common characteristics, including high vegetable intake, regular physical activity, low stress, and strong familial and community support for the elderly, all of which contribute to the capacity to live longer.Despite the impact of genetics, the heritability of lifespan remains relatively low even at higher ages. This presents a challenge in genetic studies, as there are often many phenocopies (individuals with similar characteristics due to environmental factors, not genetics) in the population of highly aged individuals. Consequently, genetic and molecular research has focused on families with a clustering of longevity, revealing common biological markers and traits associated with healthy aging, as previously observed in animal models.

5. Phenotypic and molecular studies in longevous families. Clustering of longevity within families has been observed, particularly among the top 5% of longest-lived individuals, suggesting that selecting cases from this group is optimal for large-scale genetic studies. Research has estimated the heritability of living to at least 100 years to be 0.33 in women and 0.48 in men in longevous families. Parents who belong to the top 1% of survivors in their birth cohort have a 2.3 times higher chance of having children who also fall within the oldest 1% of their birth cohorts. Additionally, nonagenarian siblings and their first-degree relatives were found to live significantly longer than the general population and show reduced morbidity in middle age.Phenotypic and molecular studies have explored potential mechanisms contributing to familial longevity. Molecular investigations of centenarians and long-lived families revealed that they exhibit relatively healthy or youthful profiles across various omics measures, including metagenomic and inflammatory profiles. Families with exceptional longevity often display immune-metabolic health profiles that are quite opposite to those associated with metabolic syndrome. This was demonstrated in studies comparing the offspring of nonagenarian sibling pairs (Leiden Longevity Study) and Ashkenazi Jewish centenarians (Longevity Project) with control groups of similar age

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and body composition.Key clinical markers for long-lived families include low glucose levels, better insulin sensitivity, low free T3 and TSH levels, large LDL and HDL lipoprotein particles, and high adiponectin levels. These families also exhibit superior immune responses, improved glycosylation patterns, and reduced immunosenescence compared to controls. Research by Passtoors et al. reported altered gene expression in the mTOR pathway in longevity families, akin to observations in animal models with extended lifespans. Furthermore, improved autophagy activation in the CD4+ T-cell compartment and enhanced T-cell functional parameters were observed, suggesting that proteostatic and regulatory processes contribute to increased immune system fitness in longevity families.

6. Genetic determinants of health span, lifespan and longevity. Various methods have been used to identify genetic loci that regulate lifespan and contribute to age-related traits and diseases. Initially, candidate gene studies focused on common variants, often based on insights from animal models, to pinpoint genes involved in lifespan regulation. Over time, hypothesis-free approaches, such as linkage studies in long-lived families and sibling pairs, as well as genome-wide association studies (GWAS) in unrelated cases and controls, were employed to find relevant genes in human lifespan regulation. Notable examples include the Genetics of Healthy Ageing (GEHA) study and various meta-analyses of GWAS.Candidate gene studies have highlighted the APOE locus (an apolipoprotein involved in cholesterol transport in the brain) and the FOXO3A locus (a transcription factor linked to cell cycle arrest, autophagy regulation, and lifespan extension in animal models) as the most robust longevity-related loci. The APOE locus, in particular, was chosen due to its known association with coronary artery disease and Alzheimer's disease. Both genes are now recognized to influence a range of clinical outcomes in human studies.Linkage studies, including the largest ones, did not identify loci shared across independent studies, except for the APOE locus, where gender differences were observed in the linkage signals, with stronger effects in women. The effects at the APOE locus are primarily driven by two common missense variants: rs429358 (Cys130Arg) and rs7412 (Arg176Cys), which determine the functional APOE alleles: ε2 (Cys130, Cys176), ε3 (Cys130, Arg176), and ε4 (Arg130, Arg176). Among over 900 nonagenarian sibling pairs, the linkage signal was primarily influenced by an enrichment of the ε2 allele rather than a depletion of the ε4 allele.

7.Towards functional analysis of interesting genetic loci. GWAS-identified variants often have a small effect and are typically located in intergenic regions, meaning they are often found between genes. To understand how specific genetic variations at these positions influence age-related traits, functional genomic studies are necessary in both humans and animal models. This includes re-sequencing carriers of the identified susceptibility alleles to pinpoint the exact genetic variation. Transcriptomic studies can help prioritize genes near significant SNPs (single nucleotide polymorphisms), as seen in some of the studies mentioned earlier. Open-access human omics databases, which contain data from blood and tissues, are essential for these functional analyses.In-depth resequencing of candidate hits and in silico analysis of the surrounding regions can predict functional variants based on amino acid changes, transcription factor binding motifs, microRNA binding sites, or splicing patterns. This helps prioritize candidate variants for further analysis using

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integrated in vivo models (such as animal models and cell models, including induced pluripotent stem cells or iPSCs) and in silico assays. Advancements in this field rely on the availability of open-source data, collaborative efforts to harmonize omics data from various cohorts, and the application of intervention studies and experimental challenges to cells and subjects. These efforts create pipelines for computational and systems biology applications.An example of functional analysis in longevity research is the study of the insulin/IGF1 signaling pathway, which has been linked to lifespan extension in animal models and is being explored as a potential candidate pathway in humans. After sequencing analysis, two mutations in the insulin receptor locus (IGF1R)—Ala-37-Thr and Arg-407-His—were found to be enriched in Ashkenazi Jewish centenarians compared to controls. These mutations were associated with reduced activity of the IGF1 receptor in immortalized lymphocytes and attenuated IGF1 signaling in mouse embryonic fibroblasts (MEFs) in a mouse Igf1r null background. The findings suggested that MEFs expressing the human longevity-associated IGF1R mutations showed diminished IGF1 signaling and a reduced physiological response to cell proliferation signals, indicating a potential mechanism through which these mutations may contribute to longevity.

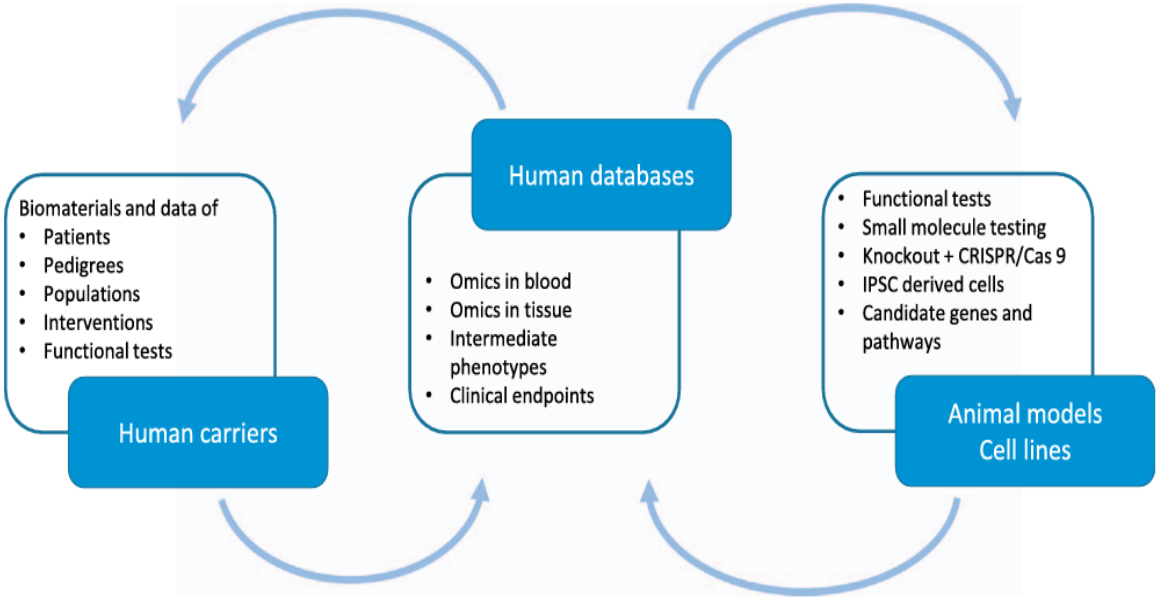

Fig. 2. Schematic presentation of cross-species pipeline of functional genomic studies.

8. Conclusion

In conclusion, despite significant efforts to identify genetic loci associated with human longevity, functional follow-up studies using elaborate cell and animal models are still limited, especially for most GWAS-identified loci. However, the numerous suggestive loci discovered in studies related to lifespan phenotypes, epigenomes, and transcriptomes may point to overlapping novel pathways that could align with interesting quantitative trait loci (QTLs) observed in animal models of aging. The functional interpretation of these intergenic regions associated with lifespan regulation requires deeper insights into genome and systems biology, as well as the development of computational biology approaches.Burden analysis in whole-genome sequencing studies, aimed

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at identifying loci enriched for mutations in the oldest-old, would benefit from increased study power and more carefully selected subjects, ideally from families with a history of longevity across multiple generations. The use of molecular and physiological age predictors in genetic studies offers a promising approach to map loci involved in biological aging at the tissue and system levels.To reach consensus on the most relevant biological age predictors for genetic studies and to improve the classification and risk prediction of vulnerable elderly populations, more consistent data collection across studies is needed. Increasingly, clinical studies focusing on age-related organ failure are incorporating molecular insights into aging biology, such as markers of senescent cells, metabolism, telomere length, and epigenetic changes, to define molecular and phenotypic hallmarks of aging in organs like the kidney, lung, heart, and brain.To better understand the heterogeneity in aging processes, it is essential to compare data on age predictors across repeated molecular and phenotypic measures taken over the life course in longitudinal studies. By measuring biomarkers dynamically—through repeated challenges and prolonged exposure periods—we can better link molecular vulnerability or resilience to functional and clinical resilience, shedding light on how individuals age differently and how interventions may help mitigate age-related decline.

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