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Review Article

From Biological Age to Clinical Phenotype: State of the Science in DNA Methylation, Multi-Omic Clocks, and Translational Utility

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Abstract

Background: Chronological age remains an imprecise surrogate for biological risk, motivating the development of molecular "biological age" metrics that integrate DNA methylation, genetic, and multi-omics data to quantify physiological decline and disease susceptibility. Epigenetic clocks, beginning with Horvath and Hannum and evolving through various iterations, have demonstrated strong associations with morbidity and mortality. Recent advances extend these approaches to multi-omics frameworks incorporating Polygenic Risk Scores (PRS), metabolomics, and organ-specific biomarkers, yet translation into clinical use remains limited by issues of reproducibility, ancestry bias, and regulatory readiness.

Methods: This review synthesizes the analytical foundations, validation evidence, and translational progress of current biological age technologies. We evaluated exemplars spanning first-generation methylation clocks to next-generation multi-omic systems, emphasizing analytical validity (precision, stability, reproducibility), clinical validity (association with disease and mortality), and clinical utility (decision support and cost-effectiveness). We further identified evidence gaps related to cross-ancestry performance, standardization of pipelines, and ethical frameworks for equitable implementation.

Results: Across studies, methylation-based biomarkers show reproducible associations with health span and lifespan outcomes and demonstrate moderate responsiveness to lifestyle and pharmacologic interventions. Multi-comic models integrating genetic, epigenetic, and phenotypic data capture organ-specific aging patterns and reveal differential vulnerabilities across systems such as neurocognitive, cardiometabolic, and immune domains. However, inter-laboratory variation, incomplete validation in diverse populations, and the absence of standardized reference materials continue to constrain clinical deployment. Integration of PRS offers additional mechanistic insight into inherited susceptibility but requires rigorous ancestry calibration and bias assessment to prevent inequitable translation.

Conclusions: Biological age technologies represent a transformative but still maturing frontier in precision health. Realizing their potential will require coordinated, multi-site efforts encompassing reproducibility studies, prospective clinical trials, and regulatory alignment. Establishing minimal clinically important differences, validated reference standards, and transparent reporting frameworks will be critical for acceptance in clinical and regulatory contexts. Platforms incorporating genetic predisposition and methylation dynamics illustrate the direction of current innovation, but definitive clinical validation and equitable access remain the cornerstones for responsible translation.

Keywords: Biological age, DNA methylation, Epigenetic clocks, Polygenic Risk scores, Multi-omics, Biomarker validation, Reproducibility, Regulatory science, Translational aging, Clinical utility

Introduction

Chronological age, i.e., time elapsed since birth, remains the dominant descriptor of risk in clinical medicine, yet it incompletely captures heterogeneity in physiological reserve, disease susceptibility, and treatment responsiveness [1]. Molecular "biological age" metrics derived from DNA methylation and other omic layers aim to quantify the accumulated effects of genetics, environment, and lifestyle on organismal aging [2]. Thus, biological age offers the potential for earlier detection of risk, stratified prevention, and objective monitoring of intervention effects [3]. The historical development of epigenetic clocks began with first-generation methylation predictors that estimate chronological age from CpG methylation patterns (Horvath, Hannum), demonstrating the feasibility of using the methylome as a molecular chronometer [4]. These foundational clocks established that methylation at specific CpG loci correlates tightly with chronological age across tissues and laid the groundwork for subsequent biomarkers optimized for clinical outcomes rather than merely calendar time [5]. Subsequent generations of clocks shifted focus from chronological prediction toward health span and lifespan relevance. Phenotypic and mortality-trained clocks (for example, PhenoAge and GrimAge) incorporate clinical and biomarker information during training and show substantially stronger associations with morbidity and mortality than the original chronological estimators. These second-generation measures therefore provide improved prognostic signal for clinical endpoints and are better suited for translational applications such as risk stratification and surrogate outcome development (Box 1).

BOX 1. INTERPRETING "BIOLOGICAL AGE": SEMANTICS, STATISTICS, AND CLINICAL MEANING

Semantics:

- *Chronological age* is time since birth; *biological age* is a statistical construct derived from molecular and phenotypic data.
- Different platforms (epigenetic clocks, EBPs, multi-omic panels) may use the term "biological age," but each reflects distinct underlying biology and assumptions.
- Reports should clearly specify whether the output is an age predictor, a rate-of-aging score, or an organ/system-specific metric.

Statistics:

- Biological age measures are built using regression, survival, or machine learning models. Each has different training outcomes (chronological age, mortality, disease events), which shape interpretation.
- Outputs may be expressed as age acceleration (Δage), percentile relative to peers, or standardized scores. These are relative metrics, not absolute truth.
- Test–retest reliability, measurement error, and cohort calibration are critical for interpreting changes over time.

Clinical Meaning:

- Biological age is best understood as a risk stratification tool: individuals with accelerated age have higher probability of adverse outcomes, not a deterministic prognosis.
- Organ-system or pathway-specific "ages" may map more directly onto symptom clusters (e.g., motor decline, immune resilience).
- Clinically actionable use cases today are limited to research, trial enrichment, and monitoring response to interventions. Widespread adoption requires validated minimal clinically important differences (MCID), reference ranges, and outcome-linked thresholds.

A newer frontier expands beyond single-purpose clocks to multi-omic and system-level frameworks that integrate SNPs, Polygenic Risk Scores (PRS), CpG signatures, metabolomic proxies, and clinical phenotypes [6]. Examples include systems-based methylation clocks that aim to capture differential aging across organ systems and Epigenetic Biomarker Proxies (EBPs) that serve as methylation-derived surrogates for serum proteins, metabolites, and clinical traits [7]. These integrated approaches

open the possibility of organ-specific "ages," mechanistic biomarker discovery, and more actionable reports for clinicians and trialists.

However, broad clinical translation demands rigorous validation in symptomatic, multi-system cohorts and across diverse ancestries. Measures must demonstrate analytical validity (precision, stability, cross-lab reproducibility), clinical validity (association with incident disease, disability, and mortality), and clinical utility (improved decision making, outcomes, or cost-effectiveness) before adoption beyond controlled research settings. Newer tools such as Dunedin PACE, designed to quantify the pace of aging and optimized for intervention trials, illustrate progress toward responsive biomarkers, but large multi-site replication and standardization efforts remain priorities [8]. This review synthesizes the current technology landscape (from single-site CpG clocks to multi-omic systems age models), examines analytical and clinical evidence across exemplars, and proposes a research and regulatory roadmap to move biological age measures from promise to practice.

Technology Landscape and Analytical Pipelines. Ensuring the validity and reproducibility of biological age measures requires meticulous attention across the full analytical pipeline, beginning with sample acquisition and pre-analytics, where specimen integrity is paramount; venous whole blood and saliva remain the most common sources, and optimization must target test–retest precision, stability, and minimization of batch effects using rigorous QC metrics (e.g., call rate, extraction yield, degradation markers) [9]. Genotyping spans from array-based platforms to Whole-Genome Sequencing (WGS) and low-coverage WGS, with analytic validity dependent on accurate imputation, stringent call-rate thresholds, and concordance across platforms to ensure reproducibility across laboratories [10]. DNA methylation profiling, central to epigenetic aging research, currently employs Illumina array platforms (450K, EPIC, EPICv2) or sequencing-based methods, with pipelines requiring normalization (Noob, BMIQ), probe filtering, and cell-type deconvolution to mitigate technical variation and cellular heterogeneity [11], [12]. Beyond methylomics, multi-modal biomarker modalities provide complementary information: immune resilience (cytokine panels, lymphocyte subsets, receptor repertoire diversity), metabolic/nutritional status (metabolomics, micronutrients, lipidomics), mitochondrial integrity (mtDNA copy number, oxygen consumption surrogates, NAD(H) metrics), systemic inflammation and oxidative stress (CRP, IL-6, F2-isoprostanes, oxidized LDL, GSH/GSSG), functional and genetic proxies of physical performance (e.g., ACTN3 variants), and environmental/food sensitivity assays (IgE/IgG), though the latter remain analytically controversial [13-16]. Integrating such heterogeneous data necessitates data fusion and feature engineering approaches capable of addressing scale differences, correlation structures, and temporal dynamics, leveraging dimensionality reduction, multi-omic integration, and longitudinal modeling frameworks [17]. Building predictive model classes for biological age has involved penalized regression (elastic net), ensemble learning (gradient boosting, random forests), deep learning architectures, and survival models (Cox regression, DeepSurv), while PRS require rigorous evaluation for cross-ancestry transferability to avoid exacerbating health disparities [18,19]. Finally, to achieve translational rigor, reproducibility and version control are non-negotiable: pipelines must embed MLOps practices including model versioning, standardized code, logging, and audit trails to enable transparent deployment in clinical and regulatory settings, aligning with best practices for computational diagnostics [20,21].

Epigenetic Aging Technologies and Biological Age: Exemplars and Evidence

Epigenetic aging technologies have rapidly diversified, with several platforms advancing from proof-of-concept methylation clocks toward clinically relevant biomarkers of biological age. The MGB Aging Biobank clock leverages 1,068 CpG sites with demographic percentile logic and has been disseminated via preprints and academic presentations, while Symphony Systems Age, developed in the Yale cohort, incorporates approximately 11,000 CpGs with percentile-based scoring [22]. Among the most influential, the aforementioned DunedinPACE, compresses information from 173 CpGs (normalized against ~40,000 CpGs) into a single-timepoint measure of the pace of aging, and has shown robust associations with morbidity, disability, and mortality across multiple validation studies[8,23]. Expanding beyond clocks, Epigenetic Biomarker Proxies (EBPs) utilize >25,000 CpG sites across large cohorts (e.g., MGB Aging Biobank, Generation Scotland, Framingham Heart Study, Alzheimer's Disease Neuroimaging Initiative) to model disease-specific risk, with exemplars such as a demyelination proxy (odds ratio 0.27, replicated at Ohio State University) and validated associations with cardiovascular disease and Alzheimer's pathology, offering advantages over serum biomarkers by averaging temporal signals and reducing short-term variability [23,24]. Collectively, the evidence around epigenetic clocks reflects a generational trajectory: first-generation clocks (Horvath, Hannum) achieve accurate prediction of chronological age but limited clinical sensitivity;25 second-generation mortality-linked clocks (PhenoAge, GrimAge, DunedinPACE) integrate phenotypic and risk factor features, yielding stronger predictive value for healthspan and survival; [25,26,27] and newer iterations target the rate of aging, thereby increasing responsiveness to interventions. Responsiveness to lifestyle and pharmacologic interventions, including diet, exercise, sleep optimization, and stress reduction, is increasingly documented, though effect sizes remain variable and replication is required to establish robustness across cohorts [28,29]. Critical challenges persist tissue specificity versus blood-based surrogates complicates interpretation, Minimal Clinically Important Differences (MCID) and test–retest reliability remain under evaluation, and external validity across diverse ancestries, age groups, and comorbidity profiles is incomplete, given that many clocks were trained in European ancestry populations, raising concerns of transferability and bias [19,30].

These limitations underscore the need for standardized pipelines, multi-ethnic validation, and harmonized metrics to advance epigenetic clocks from promising research tools into clinically actionable endpoints.

Analytical Foundations

The analytical foundation of epigenetic aging technologies hinges on rigorous design choices at each stage of data generation and processing. A central step involves CpG site selection, which varies substantially across exemplars, from targeted panels of several hundred CpGs in early clocks to >10,000 sites in second-generation models and proxy frameworks, balancing parsimony with predictive accuracy [25], [26]. Downstream, normalization strategies such as the sesame pipeline and its open-source implementation openSesame are widely employed to correct background, dye biases, and technical variation, while applying stringent QA/QC procedures that include thresholds for DNA yield, bisulfite conversion efficiency, probe-level filtering, dye-bias correction, batch harmonization, and concordance of sex annotation and methylation patterns; age deltas from established clocks are often used as an internal validity check [12,31]. These pipelines aim to maximize reliability, a critical consideration given the transition of clocks from research settings toward clinical endpoints. Notably, methylation-based biomarkers demonstrate lower intra-individual variability than many serum biomarkers, with stability profiles analogous to HbA1c. Such stability profiles reflect cumulative biological processes over time rather than transient fluctuations, thereby offering greater robustness for risk stratification and longitudinal monitoring [32,33]. Collectively, these analytical practices form the foundation for establishing the precision, reproducibility, and interpretability of biological age measures.

Organ-System Aging, Functional Domains, and Clinical Validity

Aging is not uniform across organ systems; rather, it reflects a mosaic of differential vulnerabilities shaped by genetic, epigenetic, metabolic, and environmental influences. Recent advances in multi-omic profiling have enabled the construction of organ-specific "clocks" and functional indices that map CpG, SNP, and transcriptomic features to domains such as brain, heart, liver, kidney, immune, endocrine, musculoskeletal, skin, gastrointestinal, pulmonary, and reproductive systems. These models provide a conceptual framework for quantifying organ-specific decline and capturing multi-system dysregulation indices that better reflect real-world trajectories of health span and disease risk. Studies have developed and validated organ-targeted aging clocks (e.g., neuroepigenetic, cardiovascular, hepatic) and composite panels. Convergent validity is demonstrated by correlations with established clinical measures such as VO_2max and DEXA (musculoskeletal), Pulmonary Function Tests (PFTs), and neurocognitive batteries (cognition). Such approaches not only highlight differential aging across systems but also allow for construction of multisystem burden scores-quantifying the extent to which one system's acceleration contributes to global biological age.

Immune system aging plays a central role in mediating vulnerability to disease. Panels integrating cytokines, methylation signatures, and oxidative stress markers show analytical validity and strong associations with epigenetic age acceleration. Clinical outcomes include infection severity, vaccine responsiveness, and recovery from physiological stressors. Interventional studies targeting inflammatory and oxidative pathways, through pharmacological agents, stress reduction, or lifestyle interventions, demonstrate measurable shifts in biological clocks, supporting causal relevance.

Metabolomic profiling reveals signatures of aging reflected in nutrient status, lipidomics, and amino acid metabolism. Mitochondrial measures, such as mtDNA copy number (mtDNA-CN) and respiration capacity proxies, are increasingly integrated into aging clocks. Dietary, fasting, and exercise interventions produce reproducible reductions in biological age estimates, with effect sizes ranging from modest to clinically meaningful depending on intensity and adherence. This emphasizes mitochondria as both sensors and effectors of biological aging. Epigenetic signatures of environmental toxicants (e.g., air pollution, heavy metals) and psychosocial stress have been consistently detected across cohorts, linking exposome burden to biological age acceleration. Composite resilience indices incorporating stress biology markers enhance predictive accuracy. Emerging workplace and lifestyle interventions-ranging from green-space exposure to structured stress-reduction programs-demonstrate biological age impacts, highlighting modifiability of environment–epigenome interactions.

Clinical Validity: Linking Biological Age to Phenotypes

The ultimate test of these approaches lies in their connection to lived experience and clinical outcomes. Symptom clusters map coherently onto biological age outputs, providing functional anchors:

a) **Motor and coordination**: Preliminary associations link balance issues, tremors, and clumsiness with cerebellar and basal ganglia vulnerability, as suggested by exploratory analyses of demyelination proxies and neurological clocks. These associations remain hypothesis-generating rather than diagnostic.

b) **Speech and swallowing:** Dysarthria, dysphagia, and fine motor writing (~7 mentions) reflect cranial nerve and sensorimotor decline, relevant to neuromotor age estimates.

c) **Cognition and learning:** Difficulties in learning, distractibility, and slowed response (~11 mentions) converge with cognitive decline signatures validated in ADNI-based EBPs.

d) **Memory:** Short-term memory loss (~4 mentions) aligns with hippocampal atrophy and methylation signatures tied to Alzheimer's disease risk.

e) **Seizures and neurological events:** Grand mal seizures and collapse spells (~3 mentions) may connect to mitochondrial and demyelination biomarkers.

f) **Vision and eye movement:** Vertical gaze palsy and peripheral vision loss (~5 mentions) provide rare but sensitive indicators of neurodegenerative aging, outside the scope of typical chronological clocks.

g) **Psychiatric and behavioral:** Paranoia, delusions, and poor social skills (~5 mentions) are consistent with stress-biology methylation markers and resilience indices.

h) **Other systemic symptoms:** Headaches, fatigue, and hearing loss (~3 mentions) highlight the interplay between multisystem dysregulation and biological age acceleration.

Together, these domains underscore how epigenetic clocks and omics-derived biomarkers provide a clinically interpretable bridge between molecular signatures of aging and functional decline across organ systems. By situating composite biological age readouts within symptom clusters and natural history trajectories, this framework supports both mechanistic insight and translational relevance for risk stratification, early intervention, and monitoring of therapeutic response.

Clinical Validity, Utility, and Translation

Aging biomarkers derived from epigenetic clocks, organ-system panels, and composite multi-omic indices are increasingly evaluated not only for their validity as predictors of health span and lifespan but also for their clinical utility as decision-support tools in prevention, disease monitoring, and therapeutic development. Robust evidence links biological age acceleration to a wide range of hard outcomes, including incidental disease, disability, mortality, and quality-of-life endpoints across diverse populations. Comparative analyses suggest that Epigenetic Biomarker Proxies (EBPs) may approach the prognostic value of established metrics in certain research cohorts. For example, early studies indicate that MS EBPs demonstrate predictive power in line with MRI, while CVD EBPs show similar associations to LDL cholesterol as risk markers. In neurodegenerative disease, EBPs from the ADNI cohort have shown promising results in research contexts, though regulatory acceptance as clinical endpoints is pending. Beyond cross-sectional associations, longitudinal studies highlight the prognostic vs. predictive value of different clocks, with net reclassification improvement analyses providing quantitative benchmarks for clinical adoption. Importantly, external validity has been tested across ancestry groups, sex, socioeconomic strata, and comorbidity profiles, though continued efforts are needed to avoid bias and ensure global generalizability.

Translation of biomarker outputs into actionable insight requires alignment with symptom clusters and organ-system decline. Biological age reporting enables trial enrichment (identifying high-risk subgroups more likely to experience events), therapy monitoring (tracking biological responses to interventions), and surrogate endpoint testing (where validated). Composite omic platforms are particularly promising for linking molecular signatures to functional symptom domains (e.g., demyelination EBPs mapping to motor dysfunction, or neurodegenerative EBPs mapping to cognitive decline). These connections allow clinicians and researchers to move beyond abstract "biological age" estimates to granular, disease-relevant readouts that inform prognosis and intervention timing.

A key determinant of adoption is whether decisions informed by biomarker reports lead to measurable health gains or cost savings. Early studies suggest that integrating EBPs into clinical care pathways may improve adherence to preventive interventions, reduce downstream costs, and allow for precision targeting of costly therapeutics. Formal cost-effectiveness modeling, accounting for thresholds, payer perspective, and time horizons, is still nascent but critical. In the context of clinical trials, the use of biological age readouts for enrichment, surrogate endpoints, and responder identification has potential to reduce sample sizes, shorten timelines, and increase statistical power.

Widespread deployment of aging biomarkers requires careful attention to psychological, ethical, and social implications. Feedback on accelerated biological age may cause distress or disengagement if not paired with mitigation strategies and actionable recommendations. Governance frameworks must prioritize data privacy, consent, and secure handling of multi-omic plus AI-derived profiles, potentially leveraging federated learning and differential privacy. Addressing bias and fairness is essential: models must be explicitly validated across ancestry groups to avoid perpetuating inequities, and deployment must consider access, affordability, and the digital divide to prevent restricted benefit to privileged populations.

Evidence Gaps, Research Priorities, and Translation Pathways

Despite rapid advances in epigenetic clocks, multi-omic biomarkers, and composite risk models, substantial gaps remain in establishing validity, utility, and safe deployment at scale. Addressing these challenges requires coordinated investment across discovery, validation, regulation, and implementation. Integration of PRS with methylation and clinical data offers promise for refining individualized risk prediction. However, pipelines for PRS construction require ancestry calibration and portability testing, as performance often drops in non-European cohorts. Combining PRS with epigenetic clocks and clinical covariates in integrated models is a promising approach for cardiometabolic disease, neurodegeneration, and cancer predisposition, but raises

challenges in communicating risk vs. actionability to patients. Ethical frameworks must clarify boundaries between actionable prevention vs. deterministic messaging.

For aging biomarkers to be trusted in clinical or regulatory contexts, rigorous demonstration of precision, accuracy, and reproducibility is essential. Key priorities include: 1) establishing intra-/inter-assay coefficients of variation, limits of detection/quantification, and cross-laboratory reproducibility; 2) systematically quantifying batch effects, validating performance across storage conditions and freeze–thaw cycles, and developing reference control materials; and advancing harmonization and standardization, including shared reference panels, calibration procedures, and benchmarking datasets to support cross-platform comparability. Translation into routine care will also require alignment with evolving regulatory frameworks. At present, most tests are validated under CLIA as Laboratory-Developed Tests (LDTs). While broader FDA oversight is possible in the future, no clearance has yet been granted, and clinical claims should therefore be considered premature.

Evidence Gaps and Research Agenda

Several areas of evidence remain underdeveloped and require targeted research investment:

a) **Symptomatic cohorts:** Expansion of validation in patients with neurological, psychiatric, or multisystem disorders (e.g., phenotype datasets with motor, cognitive, psychiatric manifestations) to align biological age with lived clinical experience.

b) **Percentile logic and reference ranges:** Harmonization of percentile algorithms across platforms, and establishment of reference values for organ-system–specific "ages."

c) **Large, diverse cohorts:** Funding for multi-site, longitudinal cohorts that integrate omics with deep phenotyping across ancestry, socioeconomic strata, and health contexts.

d) **Trial readiness:** Priority RCTs to evaluate interventions' effect sizes on biological age, alongside definition of core outcome sets and MCID.

e) **Methodological innovations:** Improved causal inference, mediation analysis, and longitudinal modeling, alongside open science efforts such as reference datasets, benchmarking challenges, and minimal reporting sets for AI-driven models (TRIPOD-AI, CONSORT-AI).

f) **Standards and pre-registration:** Harmonized analytic pipelines, preregistered protocols, and structured data/model sharing to reduce bias and enhance reproducibility.

Discussion

The integration of multi-omic biological age measures with clinical phenotype data provides an emerging framework for resolving system-level patterns of decline and disease susceptibility with unprecedented granularity. Current exemplars offer compelling proof of concept, showing that blood-based methylation and proxy panels may approach the predictive performance of traditional biomarkers and imaging endpoints in research contexts. These advances underscore the potential utility of such measures for trial enrichment, therapy monitoring, and early risk stratification. However, translation into clinical practice requires careful balance between promise and proof. Robust validation in diverse, symptomatic cohorts, reproducibility across laboratories, and harmonization of analytic pipelines remain essential prerequisites for credibility and regulatory acceptance. Absent such standards, premature deployment into consumer-facing "wellness" markets risks eroding scientific trust and conflating exploratory research tools with clinically validated diagnostics. Clear delineation between research-grade and commercial applications is therefore critical to ensure responsible and equitable translation. Implementation today may be justified in research settings, early-phase trials, and carefully defined high-risk populations, where biological age measures can accelerate discovery while safety, ethics, and equity guardrails are maintained. The roadmap to definitive evidence will require coordinated work across multi-site cohorts, randomized controlled trials, formal cost-effectiveness analyses, and regulatory engagement to establish validated thresholds for clinical decision-making. Beyond traditional analytical and clinical validity, priorities include: (i) assay precision and stability studies with predefined acceptance criteria (e.g., *intra-/inter-assay* CVs, freeze–thaw and storage robustness), (ii) inter-laboratory ring trials and external quality assessment to demonstrate cross-site reproducibility, (iii) harmonized preprocessing/modeling pipelines with version control and audit trails, (iv) calibration studies that define Minimal Clinically Important Differences (MCIDs) and actionable cut points, and (v) prospective analyses reporting discrimination, calibration, and net reclassification improvement against standard of care. To support equitable translation, validation should be powered across diverse ancestries, age ranges, and comorbidity profiles, with explicit tests of model transportability, bias, and fairness. Transparent practices, pre-registration, data/model sharing where feasible, and adherence to reporting standards (e.g., TRIPOD-AI/CONSORT-AI), will further reduce risk of overstated claims. Within this broader framework, genetic predisposition should be treated as one complementary layer among others (e.g., polygenic risk profiling combined with methylation and clinical features) to help explain inter-individual variability in aging trajectories. Any platform implementing this integration should undergo independent, multi-ethnic validation and demonstrate incremental value over existing benchmarks before clinical positioning. Clear delineation between research-use evaluation and clinical claims, together with careful communication to avoid conflating exploratory findings with approved indications, is essential for responsible and durable translation.

Integration of PRS with methylation and clinical data adds an upstream genomic layer to understanding biological aging susceptibility. This combined framework can help clarify how

inherited genetic risk interacts with epigenetic and environmental influences to shape aging trajectories. While these integrative models show promise for refining individualized risk prediction in cardiometabolic, neurodegenerative, and oncologic disease contexts, they remain exploration and must be rigorously validated before clinical use. PRS performance varies substantially across ancestry groups, underscoring the need for systematic calibration, portability testing, and bias assessment to ensure equitable translation. Integration of PRS with methylation and clinical data provides an upstream genomic dimension to the study of biological aging, helping to capture how inherited susceptibility, epigenetic regulation, and phenotypic state interact. As an illustrative example, AgeCode (*https://agecode.bio/master/home/*) combines genomic sequencing, methylation measures, and multi-system biomarker profiling in a commercial test, though its clinical utility and validation across diverse populations remain subject to rigorous independent evaluation .In summary, biological age technologies represent an important and rapidly evolving field with genuine translational potential, yet their success will hinge on adherence to rigorous scientific standards, transparent communication of uncertainty, and deliberate efforts to achieve inclusivity and equity in validation and access.

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Ethics Declaration

All authors declare that there are no ethical declarations to declare in relation to this manuscript.

Competing Interests

None.

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