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To cite this article: Abner T. Apsley, Laura Etzel, Qiaofeng Ye & Idan Shalev (16 Dec 2025): From population science to the clinic? Limits of epigenetic clocks as personal biomarkers, Epigenomics, DOI: [10.1080/17501911.2025.2603880](https://doi.org/10.1080/17501911.2025.2603880)

To link to this article: <https://doi.org/10.1080/17501911.2025.2603880>



Published online: 16 Dec 2025.



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PERSPECTIVE



From population science to the clinic? Limits of epigenetic clocks as personal biomarkers

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ABSTRACT

Epigenetic clocks are machine-learning algorithms which use DNA methylation patterns to predict aging-related phenotypes, such as chronological age, composite indicators of health, time-to-death, and the pace of biological aging. These clocks have been instrumental at the population level in revealing how disease risk emerges from behavioral, environmental, and psychosocial factors, and how certain anti-aging interventions may alter those trajectories. Given the success of epigenetic clocks at the population level, it is reasonable to assume they might also hold value as individual-level biomarkers. We contend, however, that fundamental technical and biological properties of these algorithms prohibit their current use at the individual level. Technical concerns include methods of clock construction, sample collection and processing, data preprocessing, and computational implementations. Biological considerations include the nature of DNA methylation and its dynamics, variation across developmental periods, tissue specificity, and sensitivity to environmental/sociodemographic contexts. We show that clocks fail to meet common standards for clinical utility compared with established biomarkers, and that applying epigenetic clocks in individual-level decision making can be uninformative and potentially harmful. Finally, we argue that even if all technical and biological hurdles can be overcome, epigenetic clocks, as we currently understand them, should not be used to make individual-level decisions.

PLAIN LANGUAGE SUMMARY

Epigenetic clocks are tools that estimate your age by looking at chemical markers on DNA. They have helped researchers understand how things like lifestyle, environment, and health habits affect aging across large groups of people. However, they are not reliable for use on a single person. Unlike common medical tests, epigenetic clocks do not meet the usual standards for accuracy in healthcare. Using them to guide personal health or economic choices could be confusing or even harmful.

ARTICLE HISTORY

Received 10 June 2025
Accepted 10 December 2025

KEYWORDS

Epigenetic clocks; DNA methylation; biological aging; machine learning; translational science; biomarkers

1. Introduction

Epigenetic clocks are machine learning algorithms trained to predict “biological age” from patterns of DNA methylation (DNAm) [1]. By analyzing methylation levels at hundreds to thousands of cytosine-phosphate-guanine (CpG) sites across the genome, these models generate estimates of biological age that often meaningfully diverge from chronological age. Over the past decade, dozens of such clocks have been developed to capture various aspects of the aging process, from all-cause mortality and disease risk to responsiveness to lifestyle interventions and cellular stress [2].

At the population level, epigenetic clocks have proven to be powerful research tools: they predict age-related outcomes above and beyond chronological age [3–5], exhibit sensitivity to aging interventions [6], and even quantify the pace of aging over time [7]. Age-related signals from these clocks have been observed in a variety of studies and cohort sizes. Their success has led to growing excitement about their potential use in individual-level contexts, both clinical and consumer-facing. Companies now market epigenetic age testing directly to consumers, while some

researchers and clinicians advocate for their eventual use in diagnostics and personalized medicine.

In this perspective, we argue that this translational leap, from population-level use to individual-use, represents a fundamental misunderstanding of what these tools were designed to do, and what they can reliably measure. Framing clock outputs as “individually-actionable” blurs the line between research and clinical care, inviting misuse in ways that could reinforce bias and undermine equitable health policy. We caution against the hasty adoption of these measures for individual use and detail potential risks of doing so. To support our argument, we examine the conceptual and technical limitations that preclude clocks from becoming reliable individual-level biomarkers, assess their performance against clinical utility benchmarks, and describe the societal risks of adopting epigenetic clocks in personalized health and consumer settings.

Epigenetic clocks have been a boon for research across social science and health domains; however, there remain clear opportunities for refinement. In service of the goal of refinement, we aim to foster ongoing dialogue about both the current utility and future direction of epigenetic clocks. The current perspective

Article highlights

- Fundamental technical and biological properties of epigenetic clocks prohibit their use at the individual level.
- Technical concerns include methods of clock construction, sample collection and processing, data preprocessing, and computational implementations.
- Biological considerations include the dynamic nature of DNAm, variation across developmental periods, tissue specificity, and sensitivity to environmental and sociodemographic contexts.
- Epigenetic clocks fail to meet standard criteria for clinical utility.
- Applying epigenetic clocks in individual-level decision making may be uninformative and potentially harmful.

article is written specifically to encourage scientists, clinicians, and direct-to-consumer companies, who either currently use, or are considering using epigenetic clocks in their work, to deeply think about the issues we raise and contribute their own perspectives to this dialogue. As pressure mounts to push these tools closer to broad adoption in clinical and commercial settings, the research community must refine the science and

confront the practical, ethical, and societal consequences of deploying epigenetic clocks at the level of individual lives.

2. Barriers preventing the application of epigenetic clocks to individuals

Three key barriers prevent epigenetic clocks from serving as meaningful biomarkers at the individual level: unreliable single-timepoint readings, practical infeasibility of interpreting longitudinal change, and a lack of specificity in measurement interpretations [8]. These barriers are driven by both technical and biological issues (see Figure 1(A)). Here, we use the word “technical” to refer to issues related to clock construction, data measurement and processing, and computational implementation. We use the term “biological” to refer to issues that arise from the inherent nature of the biological processes being measured (i.e., regulation of DNAm marks across the genome).

Single clock readings are often too noisy to be informative [9]. Clock scores are influenced by substantial measurement error, technical variation across labs and platforms, batch

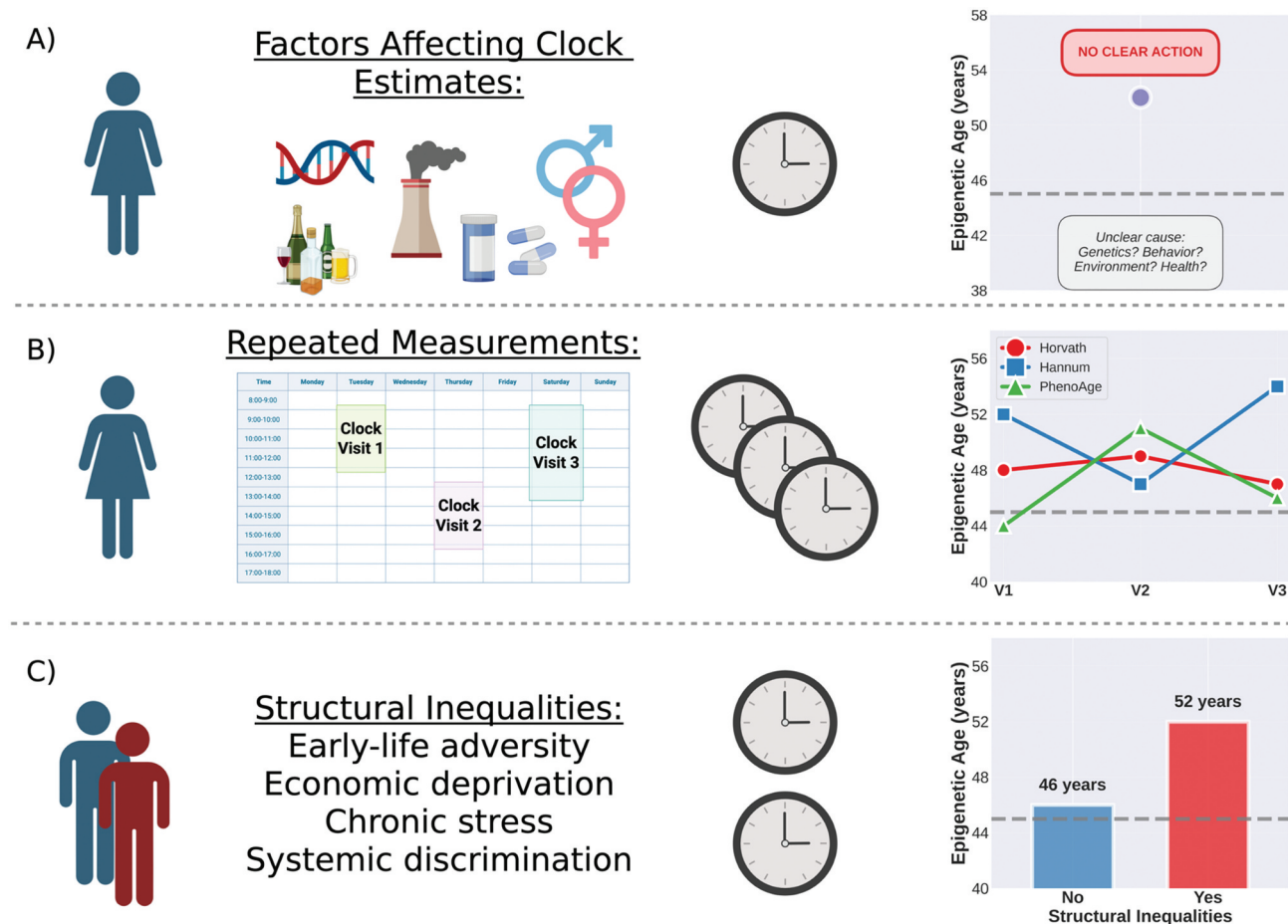


Figure 1. Challenges with individual-level applications of epigenetic clocks.

There are various reasons epigenetic clocks should not be used at an individual-level: (A) Scenario in which an epigenetic clock estimate has no technical or biological issues, yet the outcome is not meaningful due to the plethora of factors that may be influencing the estimate. (B) Scenario where an individual receives repeated measurements from an epigenetic clock within a short timeframe and observes that these measurements do not agree with one another. Furthermore, if this same individual was tested using multiple types of epigenetic clocks, each clock may exhibit varying amounts of accuracy and reproducibility across the same span of time. (C) Scenario in which two individuals with the same chronological age exhibit differences in epigenetic clock estimates due to systemic or structural inequalities. While the epigenetic clock scores may reflect some underlying differences in health, the exact reasons for these differences and the associated interventions that may be helpful are difficult to elucidate. On all plots, the gray dotted line indicates the chronological age of the individual(s) being measured. Created in BioRender. Apsley A. (2025) <https://BioRender.com/2wqxvbu>.

effects, and biological confounders like blood cell composition shifts and circadian fluctuations [10,11]. A difference in estimated epigenetic age of a year or two (the magnitude often reported by intervention studies [12]) may fall within the margin of error introduced by these sources of noise, rather than reflecting any meaningful difference in biological age. In this context, interpreting a single epigenetic clock score as diagnostic, prognostic, or requiring intervention is equivalent to acting on a weak signal buried in loud technical and biological noise.

Even if we extend the use of epigenetic clocks beyond single scores and consider that repeated measurement could theoretically provide more meaningful information, their clinical utility is fundamentally constrained by technical inconsistency. Clock estimates are highly sensitive to platform updates [13,14]. Furthermore, even subtle changes in data processing pipelines [15] can make longitudinal comparability of epigenetic age estimates nearly impossible without re-running all samples together, which renders these clocks impractical for use beyond research settings. Underlying biological factors compound these technical problems. DNAm is inherently dynamic [16], tissue-specific [17], and responsive to transient physiological events [16,18–20]. In practice, this means that an individual's clock readings can be skewed by recent illness [21], stress exposures [16,20,22], normal temporal fluctuations in DNAm levels [23–25], or medical treatments [26]. Any metric this labile to biological variability will struggle to serve as a stable anchor for individual-level decisions, no matter how sophisticated the potential technological advancements.

Furthermore, epigenetic clocks were created with the purpose of uncovering population-level associations across broad definitions of biological aging and various genetic, behavioral, health, and social variables. The definitions of biological aging used in the generation of epigenetic clock algorithms, although useful at a population level, make it difficult, if not completely impossible, to interpret clock results at an individual level. For example, if an individual was to learn that they had an accelerated epigenetic age according to a first-generation clock, what clinical interventions/treatments should be recommended for that individual? Because there is a plethora of factors that can contribute to an individual having an increased age acceleration, results from epigenetic clocks are impractical to clinical interpretation at the individual level.

We acknowledge that the field is actively working to overcome these issues and may successfully do so in the future. However, we have included a discussion of these issues here to demonstrate that the use of current epigenetic clocks for personal use is not presently feasible. In subsequent sections, we will also argue that epigenetic clocks will not be personally or clinically useful, even if all technical and biological hurdles are able to be overcome.

2.1. Technical barriers

2.1.1. Methods of clock construction

In general, epigenetic clocks have been constructed using penalized linear regression (usually elastic-net regression) to predict a chosen phenotype that represents biological age

(see [27] for a review of existing epigenetic clocks for humans). Typically, through the process of feature selection, hundreds of CpG sites are selected from thousands of sites initially fed into the training model. Each CpG site receives a model-defined weight and a linear combination of these weights is computed, thereby generating an estimate for the phenotype of choice. The choice of phenotype is foundational to the model, and clocks have been trained on a range of outcomes including chronological age, composite physiological indicators of health, time-to-death, and the rate of physiological change over time (i.e., the “pace” of aging) [7,28–31]. Importantly, these models are generally agnostic to biological mechanisms, favoring predictive accuracy over mechanistic interpretability. As a result, the CpG sites that drive predictions may be correlated with aging rather than causally involved in it, which limits their interpretability and increases their susceptibility to confounding [32,33]. This reliance on correlational rather than causal features undermines confidence in the notion that epigenetic age estimates reflect modifiable or mechanistically meaningful dimensions of aging.

Alternatively, recently developed “causal clocks” have been trained using CpG sites causally linked with healthspan-related characteristics [32]. These causal clocks have been classified as first-generation clocks because they aim to predict chronological age, and although these clocks are built using CpG sites causally linked to aging phenotypes, a recent study found they did not outperform second-generation clocks [34]. Additionally, adding these causal clocks to disease prediction models alongside age, sex, education, alcohol use, smoking, BMI, and deprivation did not improve model performance. Causal clocks also present challenges because, although they may be built on CpGs more causally related to aging processes, this does not inherently mean that they will provide actionable insights on an individual level. Therefore, although these newer causal clocks may be mechanistically linked to healthspan-related epigenetic markers, the current versions of causal clocks are not superior to standard epigenetic clocks in solving technical problems.

Compounding the issue of correlation vs. causation in the aging process, there is no consensus on the optimal biological aging phenotype to use for training a clock. Different clocks are optimized for (i.e., trained to reflect) different aspects of aging [2], and therefore often produce conflicting estimates for the same sample [17]. Without a single, standardized target, individuals and clinicians would be left to navigate a confusing array of possible interpretations. In the absence of consensus targets, causal grounding, and cross-model coherence, clock scores cannot serve as definitive indicators of biological age in personalized contexts.

2.1.2. Sample collection and processing

Variations in wet lab techniques such as sample collection [35] and storage [36,37], DNA extraction [38–40], and bisulfite treatment [41] influence the output and reliability of epigenetic clocks [9,42]. Laboratory procedures prioritize consistency and standardization to ensure minimal variation in sample treatment and processing, but this may not always be feasible, especially in clinical settings [43]. Additionally, DNAm measurements are notorious for exhibiting batch

effects which would influence the results of epigenetic clock algorithms used for individuals [11,42]. Furthermore, while individual research labs can establish standard wet lab processing protocols, the establishment and enforcement of these strict standards in both clinics and commercial entities would present a significantly greater challenge [44,45].

2.1.3. Data preprocessing

Once DNAm microarray data has been collected, there are technical factors related to data preprocessing that can influence the estimates of epigenetic clock algorithms. Here, we define “preprocessing” as all steps that occur after the initial collection of DNAm data and prior to the use of this data as an input for clock computations. In research settings, sample inclusion and exclusion criteria are often selected to ensure only high-quality samples are included in downstream analyses [46]. This includes filtering out samples with either a high percentage of CpG probes that fail detection (i.e., exhibit high detection p-values) or that show signs of poor DNA quality (i.e., have low bisulfite conversion rates leading to unreliable methylation measurements) [47,48]. The newest Illumina DNAm array (EPICv2) can be run with a minimum of 8 samples. Therefore, re-running a single failed sample in the clinic would amount to either misusing resources (if the clinical sample was not a multiple of 8) or increasing the time for individual test results to be returned due to the additional time required for samples to be collected from other patients.

Additionally, in research settings, CpG probes may be excluded if they fail detection across a sufficient number of samples (i.e., exhibit high detection p-values across samples), or have low bead counts (a marker of poor technical performance) [47,48]. However, some of these excluded probes may be integral to the functioning of clock algorithms. When such probes are removed, clock estimates may be biased or unreliable, leading to inaccurate interpretations of biological age for individuals. This could in turn bias individual-level decisions based on false negative (e.g., appearing deceptively “younger”) or positive (e.g., appearing older than the true biological state) laboratory results. Finally, the method of array normalization can also impact the outcomes of epigenetic clock estimates [15,49,50], hence clinics or commercial entities that use different normalization techniques may obtain differing results for clock estimates [51].

2.1.4. Clock computation

Computational procedures for epigenetic clocks are also highly variable and pose a barrier to effective individual use. When computing clock estimates in research settings, missing CpGs are often imputed to avoid biased estimates [52]. When individual CpGs are randomly missing across samples, common imputation methods, such as the K-Nearest Neighbor method [53], can be used to impute missing values. However, when specific CpGs are systemically missing, such as when a newer array platform is used that does not include all CpG sites from the original epigenetic clock’s training data, it is research practice to substitute missing values with average CpG values from a reference dataset. This process inherently decreases sample variation because all samples receive the same value for the missing CpG [54].

In the context of individual-level clock use, missing CpGs could arise in two key ways: they may be randomly absent due to technical variation within a given batch, or they may be systematically missing when a newer array platform omits sites used in the original clock’s training data. In the former case, imputations would vary depending on the batch, while in the latter, they would rely on a reference dataset. In both scenarios, clinics or commercial entities would need to select the reference dataset for CpG value imputations carefully by matching each individual’s age, sex, ancestry, and health status to ensure accurate imputations [17]. Failure to do so would introduce systematic biases and compromise the validity of clock-based age estimates for individuals.

2.2. Biological barriers

2.2.1. DNAm landscapes are dynamic

Although DNAm landscapes (i.e., a representation of the DNAm state of all CpG sites in the genome) were once thought to be rigid determinants of cell fate [55,56], it is now clear that these landscapes are highly dynamic [16,57–59]. Methyl residues are added *de novo* to CpG sites by the human methyltransferase enzymes DNMT3A and DNMT3B [60] and are removed through the coordinated actions of both the ten-eleven translocation (TET) enzyme family and the base excision repair pathway [61]. Both the addition or removal of a methyl group from a CpG site can arise on a timescale of minutes to hours [62,63], meaning the DNAm status of specific CpG sites can vary on similar time-scales. We demonstrated this in a study where we probed the epigenome of individuals’ immune cells across an acute laboratory stressor, finding genome-wide alterations at numerous CpG sites within 75–135 minutes [16]. Other studies computing repeated within-person clock estimates over the course of a day have also reported that these estimates exhibit significant variation [16,23,25] (see Figure 1(B)). Additional evidence for the dynamic nature of DNAm landscapes can be found in other published works [64,65].

These rapid fluctuations pose a fundamental challenge to the use of epigenetic clocks at the individual level. Efforts have been made recently to overcome this limitation, specifically by using what have been termed principal component (PC) versions of common epigenetic clocks [66]. Yet, PC versions of epigenetic clocks still exhibit oscillations across the span of a day [25]. PC clocks may be able to overcome limitations related to technical factors, but they do not overcome the fundamental biological volatility inherent in the DNA methylome. As such, the utility of epigenetic clocks as individualized biomarkers remains limited by the fluctuating nature of the biological systems they aim to quantify.

2.2.2. DNAm landscapes vary across developmental periods

Beyond the influence of short time-scale variability, DNAm landscapes also vary across developmental periods which can introduce biases. For instance, clocks trained with adult populations may exhibit significant prediction biases when used in pediatric populations. Considering the non-linear trajectories exhibited by various biomarkers across the human

lifespan [17,67], linearly extrapolating clock algorithms from an older population to a younger one will produce less accurate biological age estimates than using corresponding clocks designed specifically for a developmental period. Additionally, across development and aging, females are susceptible to periodical hormone fluctuations during both the menstrual cycle and pregnancy, as well as abrupt hormone changes leading up to menarche and menopause. Fluctuations in female hormones have been associated with acceleration or deceleration of epigenetic aging [68–70]. Because epigenetic clocks are built to maximize predictive accuracy rather than to capture biologically meaningful change, they cannot separate lasting, disease-relevant epigenetic shifts from short-term or developmental related fluctuations. This makes them unreliable tools for guiding decisions at the individual level.

2.2.3. DNAm landscapes are tissue-specific

Another biological barrier that prevents epigenetic clocks from being useful individual-level tools is that most clocks are tissue-specific. Clocks that were created using a specific tissue type (e.g., whole blood, buccal epithelial tissue, etc.) can produce inaccurate estimates, sometimes on the order of 20–30 years in difference, when applied to other tissue types [17]. These inaccuracies result from differences in DNAm landscapes across both tissue and cell types [71]. Reliance on blood-based training data is not necessarily a barrier for clinical applications, since blood draws are standard in medical practice; however, it poses a significant limitation for commercial or consumer-facing applications. Commercial and consumer tests often rely on more easily obtained tissues such as saliva or cheek swabs for buccal tissue, which have distinct DNAm profiles. If the correct tissue types were able to be used in every setting, tissue type would not be an inherent barrier to the individual use of epigenetic clocks. However, because most commercial and consumer-facing applications of epigenetic clocks are not designed to use blood tissue, this barrier presently remains.

2.2.4. DNAm landscapes are environmentally and socially sensitive

One of the most powerful aspects of DNAm-based epigenetic clocks in research contexts is their responsiveness to environmental conditions [72]. These clocks are sensitive to a wide range of exposures, such as diet, physical activity, sleep habits, smoking, stress, and even ambient pollution levels [73,74], which makes them invaluable tools for understanding how everyday behaviors and environmental contexts shape biological aging. However, this sensitivity becomes a liability when attempting to use clocks for individual-level decision making [16,26]. When a clock is this reactive to short-term states, a one-time measurement may reflect ephemeral noise rather than providing useful information about an individual's biological age. In research settings, this variability is manageable with large sample sizes and repeated measurements. In clinical or commercial settings, the cost and logistical burden of collecting multiple time-points to establish a reliable baseline clock estimate is prohibitive. As a result, clock estimates may misrepresent an

individual's aging status depending on when, where, and under what conditions their sample was collected.

Epigenetic clocks are also highly sensitive to both structural and psychosocial adversity, with their estimates often varying based on demographic characteristics such as biological sex, race/ethnicity, and the intersection of these factors with social and environmental exposures (see Figure 1(C)). Studies have documented systematic differences in clock estimates across racial and ethnic groups, including reduced predictive accuracy and biased estimates of biological age for Black and Hispanic individuals compared to White individuals, even when controlling for chronological age and other socioeconomic covariates [75–77]. Similarly, individuals exposed to early life adversity (e.g., poverty, neglect, violence, or family disruption) consistently show accelerated epigenetic aging across a range of clocks, suggesting that these measures reflect the biological embedding of adversity [78–80]. Exposure to discrimination and structural racism has also been linked to epigenetic age acceleration, particularly among Black Americans [81–83]. Applying epigenetic clocks to individual-level decisions in healthcare, insurance, or governance risks reproducing and legitimizing such existing social inequalities. In effect, clocks may encode the downstream biological consequences of social injustice while obscuring the upstream drivers, thereby reinforcing stigma or penalizing individuals for socioenvironmental conditions beyond their control.

These concerns are not hypothetical as there are already instances of direct-to consumer epigenetic age testing services marketing clocks as personal wellness metrics, and life insurance companies exploring clock-based biological age scores in actuarial risk models. Such uses risk transforming indicators of social adversity into individualized liabilities. For example, imagine an individual from a racially marginalized background whose life has been shaped by chronic discrimination and environmental stressors, factors known to accelerate epigenetic aging. Because this person's genetic ancestry is poorly represented in the datasets used to build most epigenetic clocks (see Section 4.2 for more information about reference populations), their clock results already carry additional error and bias. When an insurer interprets their elevated biological age as evidence of higher future health costs, that statistical bias is compounded and the molecular imprint of structural disadvantage is reclassified as personal risk. The result is higher premiums or loss of coverage for precisely those individuals most harmed by inequitable social conditions.

The use of epigenetic clocks for individualized health and marketplace decisions is especially dangerous compared to existing risk indicators like BMI because of the mechanistic ambiguity and perceived objectivity of epigenetic biomarkers. BMI is widely recognized as a crude proxy for health, influenced by many non-pathological factors (e.g., muscle mass, body composition, cultural differences), but epigenetic clocks carry a veneer of precision. Their complexity makes them less legible to the public and hard to contest. Reifying social gradients in molecular language risks locking in disadvantage under the guise of 'precision medicine.'

This illusion of objectivity mirrors what has already occurred in the U.S. healthcare systems. Racially biased algorithms have been used to prioritize patients for care, allocate medical resources, and predict healthcare costs, systematically disadvantaging Black patients while operating under the guise of neutral data-driven optimization [84,85]. Notable examples include the use of race-corrected algorithms in nephrology that overestimate kidney function in Black individuals, reducing their eligibility for transplant referral, and biased cost prediction algorithms that misallocate care away from high-need Black patients [86]. Even well-intentioned tools grounded in data can encode and perpetuate structural bias, and unlike more interpretable measures such as BMI or kidney function, the complexity of methylation-based scores makes their biases hard to detect, harder to explain, and easier to defend as objective truth.

Apart from these technical, biological, and ethical concerns, the clocks themselves fall short for individual use in more fundamental ways. Their performance metrics (e.g., sensitivity, specificity, predictive validity, and reliability) are well below what would be required for any biomarker used to guide decisions at the level of a single individual. In fact, their core statistical design reflects population-level correlations, not individual-level diagnostic accuracy. This makes them ill-suited by design to serve as personalized health tools, regardless of future improvements in technology or standardization. We turn next to the question of clinical utility and ask: do epigenetic clocks actually meet the basic thresholds we expect from a tool used to inform care?

3. Epigenetic clocks underperform on key metrics driving clinical utility

For a biomarker to be considered viable for individual-level use, it must meet specific clinical criteria that ensure both utility and trustworthiness in decision-making contexts [87]. These criteria include, but are not limited to: (1) a well-defined and widely accepted biological interpretation, (2) high levels of accuracy and reproducibility, (3) established clinical thresholds for interpretation, and (4) favorable cost-benefit ratios. In this section, we evaluate the potential translational value of epigenetic clocks against these clinical criteria. To contextualize these evaluations, we compare clocks to other widely used clinical biomarkers. Table 1 summarizes how epigenetic clocks and select extant clinical biomarkers compare in terms of biological meaning, accuracy, reproducibility, diagnostic utility, and cost.

3.1. Lack of consensus on the biological meaning

Epigenetic clocks were designed to quantify biological age. Though the concept of biological aging may seem straightforward, a global survey revealed that there is a lack of consensus on an aging biology paradigm [109]. In fact, this global survey reports that the only agreement reached in this field was the heterogeneous nature of the aging process [109]. Due to both the complexity and the multifaceted nature of biological

Table 1. Comparison of epigenetic clocks with common clinical diagnostic tests.

Biomarkers /Tests	Assay method	Reproducibility/Reliability		Biological meaning	Associated outcomes	Cost per sample
		Accuracy	Precision			
Epigenetic clocks	Illumina Human Methylation Microarray	MAE: ≥ 3.6 years [28,29,31]	ICC: 0.86 to 0.99 [23] CV: 2% to 10% [23]	Biological age/ biological aging pace	Mortality: HR 1.03 to 1.87 for 1 SD of biological aging acceleration [66]	\$240–\$512 [88–90]
Blood glucose	Hexokinase method	Bias $\leq 3.6\%$ [91]	CV: $<2\%$ [91,92]	Glucose metabolism	Diabetes mellitus: fasting plasma glucose ≥ 7.0 mmol/L, or OGTT ≥ 11.1 mmol/L [93].	\$1–\$2 [94,95]
HbA1c (glycated hemoglobin)	Cation-exchange HPLC	Bias $< 3\%$ [96]	CV: $<3\%$ [96]	Average blood glucose levels over 2–3 months	Diabetes mellitus: HbA1c $\geq 6.5\%$. HbA1c $\leq 7\%$ was associated with 34–76% decrease in microvascular and neurological complications, 57% decrease in CVD events, and 33% lower mortality among patients with type 1 diabetes [97].	\$5–\$8 [98,99]
Total cholesterol	Enzymatic colorimetric assay	Bias $<3\%$ [100]	CV: $<4\%$ [100]	Lipid metabolism	Hypercholesterolemia: total cholesterol >5.2 mmol/L. Higher total cholesterol is associated with higher risk of cardiovascular disease [101].	\$3–\$6 [102,103]
Creatinine	Enzymatic methods	Bias $<2\%$ [104]	CV: $<3\%$ [105]	Renal function	Elevated serum creatinine indicates renal diseases but has to be evaluated with a comprehensive physical examination [106].	\$1–\$3 [105]
Troponin I/T	High-sensitivity immunoassay	Bias: $\leq 10\%$ [107]	CV: $\leq 10\%$ [107]	Cardiac muscle injury	Elevated troponin I/T indicates acute myocardial infarction [107].	\$12–\$246 [108]

Abbreviations: MAE: Median absolute error. ICC: Intraclass correlation coefficient. HR: Hazard ratio. SD: Standard deviation. CV: Coefficient of variation. OGTT: Oral glucose tolerance test – 2 hours post 75 g glucose load. HPLC: High-performance liquid chromatography.

aging, as well as the nature of epigenetic clocks as statistically optimized algorithms [110,111], it is unlikely that epigenetic clocks capture the whole spectrum of the biological aging process. This is supported by cross-comparison studies [112,113] which indicated weak correlations among epigenetic clocks, telomere length, composite physiological aging measures, and other omics clocks designed to measure biological age. As such, epigenetic clocks do not have a clear biological meaning.

In contrast, common clinical biomarkers have clear biological meanings associated with disease diagnosis, progression, and outcomes. These biomarkers are not necessarily the cause of diseases, but they are either the most prominent features of disease presentation (e.g., blood glucose for diabetes) or very sensitive indicators of disease progression (e.g., troponin for myocardial infarction) or risk classification (e.g., serum creatinine for chronic kidney disease staging). For example, diabetes is defined as a chronic metabolic disorder characterized by persistent hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. Measurement of plasma glucose is therefore central to the diagnosis and monitoring of diabetes. Although patients with diabetes may have various complications such as cardiovascular disease, diabetic neuropathy, nephropathy, retinopathy and others, hyperglycemia is the fundamental clinical manifestation across diabetic patients. In contrast, while epigenetic clocks are often correlated with age-related outcomes, their mechanistic underpinnings, even if causative of disease, remain ambiguous [110,111]. They may capture downstream correlates or signatures of aging-related processes, but not the processes themselves. Their biological meaning is neither singular nor clearly defined, which limits their utility as clinical tools.

3.2. *Insufficient reproducibility and accuracy*

Quantitative clinical tests have high measurement reproducibility and accuracy as indicated by (1) low intra- and inter-assay coefficients of variation and (2) low bias from a common “true value,” respectively. Despite ongoing improvements, epigenetic clocks remain insufficiently accurate or reproducible for individual-level applications. As discussed earlier, clock estimates can be influenced by a host of technical and biological factors, including batch effects, array platform differences, preprocessing pipelines, and temporal instability within individuals. These sources of variation can introduce discrepancies of several years in predicted age, even when biological aging has not meaningfully changed.

The reproducibility of epigenetic clocks can be assessed by comparing the consistency of results from technical or biological replicates. In some studies, technical replicates of the same sample have produced age estimate deviations of up to 9 years [9,66]. Other studies indicate that, even at a more fundamental level, biological replicates of DNAm measurements are not as replicable as would be necessary for clinical-level use [16]. The lack of reproducibility of epigenetic clocks stems from both technical issues discussed above and the inherent dynamic nature of DNAm. As such, changes in epigenetic clock estimates across short temporal windows have been observed. Intensive repeated measurements of

epigenetic clocks could improve the signal-to-noise ratio of the estimates, but this is impractical outside of research settings.

Although some common clinical biomarkers (such as glucose or cortisol) exhibit short-term temporal fluctuations which can affect measurement reproducibility, issues with the reproducibility of epigenetic clock measurements are fundamentally different. First, the fluctuation patterns of glucose or cortisol are consistent across different individuals. Cortisol levels are highest in the morning, and glucose levels are higher after each meal. This characteristic has led to the establishment of clinical practices that require clinics to collect biospecimens at a certain time point and compare biomarker values (i.e., glucose or cortisol) against time-specific reference ranges. However, in contrast to glucose and cortisol measurements, there are no consistent circadian fluctuation patterns observed for epigenetic clocks across individuals. Additionally, circadian fluctuations in epigenetic clocks estimates seem to be clock-specific, meaning different clocks may exhibit different patterns. For example, Koncėvičius et al. [25] investigated the circadian fluctuation of epigenetic clock estimates in neutrophils from individuals 30, 52, and 54 years old. For the Horvath Pan-Tissue clock and the Teschendorff epiTOC2 clock, circadian fluctuations were observed to have the greatest amplitude for the 30-year-old individual, whereas the 52- and 54-year-old individuals exhibited only minimal variation. Furthermore, circadian fluctuations in GrimAge2 estimates were negligible in all three individuals. Such inconsistencies between both individuals and clocks would substantially complicate clinical monitoring. Second, epigenetic clock estimates are confounded by blood cell compositions which vary on an individual level [77]. In contrast, biomarkers such as glucose or cortisol are present in a cell-free manner and do not suffer from immune cell composition confounding. Third, in vivo levels of biomarkers such as glucose or cortisol can be stimulated by certain procedures such as the Oral Glucose Tolerance Test (OGTT) or the Adrenocorticotrophic Hormone Stimulation Test, which can assist in clinical diagnosis of diabetes and adrenal inefficiency [114,115]. However, no comparable procedure exists for epigenetic clocks to distinguish pathophysiological alterations from physiological fluctuations.

Importantly, even if measurement reproducibility was substantially improved, clocks still lack a clear gold standard to anchor their accuracy. Both the definition and assessment of accuracy for epigenetic clocks are more elusive than commonly used clinical biomarkers. For example, the accuracy of glucose assays is assessed by comparing a measured value against a “true” reference value that is determined using reference methods. For glucose assays, reference methods are ranked in tiers, with mass spectrometry-based methods regarded as the highest order [116,117], followed by the hexokinase method [91,118]. Certified reference materials traceable to Isotope Dilution Mass Spectrometry are used to calibrate routine clinical laboratory assays of glucose [91], with allowable total error of 8% or less regulated by the Clinical Laboratory Improvement Amendments [119]. In contrast, accuracy assessments of epigenetic clocks do not have such a rigorous system. First, biological age is a construct not a biochemical molecule. Epigenetic clock estimates are

composite scores of DNAm levels of hundreds CpG sites. Errors that are small in magnitude for individual sites can accumulate to a large bias in the final estimate. Second, there is no gold standard reference for the measurement. Various epigenetic clocks are not ranked in tiers and not a single method is recognized to generate “true” values. Even though epigenetic clocks are classified into several generations based on their purposes of prediction, there is no gold standard established for each generation of the clocks to anchor measurement accuracy. Accuracy of epigenetic clocks usually refers to the performance of clock estimates in predicting chronological age or health outcomes. No strict regulations of allowable bias are in place to determine the usability of certain epigenetic clocks for clinical purposes. Moreover, the current accuracy reports of epigenetic clocks do not appear as satisfactory. For example, the median absolute error of first-generation epigenetic clock estimates from observed chronological age values have been reported as 3.6 years or higher [28,29], although there have been recent field-specific attempts to decrease these errors [120]. For the associations of first-generation clocks with health outcomes, a 5-year increase in aging acceleration was associated with 8–15% increase in mortality risk [5]. Including epigenetic clocks into disease incidence prediction models with sociodemographic factors only improved the area under the receiver operating characteristic curve by a few percentage points [34]. While such a level of accuracy may be acceptable for population-level studies, it falls short of the precision required for clinical or commercial use.

3.3. No clear cut-off for diagnostic purposes

Clinical tests have commonly agreed upon cutoff values. For example, fasting plasma glucose ≥ 7.0 mmol/L or HbA1c $\geq 6.5\%$ supports diagnosis of diabetes [93]. Additionally, total cholesterol > 5.2 mmol/L indicates hypercholesterolemia [101]. Estimated from serum creatinine, glomerular filtration rate lower than 60 mL/min/1.73 m² for three months or more indicates chronic kidney disease [121,122]. In contrast with these diagnostic tests, epigenetic clocks do not have clear cutoff values of aging acceleration that would indicate intervention was required. Moreover, the absolute age acceleration (AAA, calculated as the difference between biological age and chronological age) suffers from a statistical phenomenon similar to “regression to the mean effect,” such that AAA always correlates negatively with chronological age, meaning older individuals are more likely to have negative AAA whereas younger individuals are more likely to have positive AAA [27]. Cutoffs based on AAA would not make sense if an individual wants to see how their age acceleration changes over time. To address this limitation in population research, relative age acceleration (RAA, calculated as the residuals of linear regression of biological age against chronological age) is more widely applied. RAA reflects how much faster or slower someone is aging relative to what would be expected for their age in a given population. However, RAA has to be calculated based on a reference population, which in essence is comparing an individual’s biological age against the mean biological

age of the reference population controlling for chronological age. The choice of reference population will affect the final RAA value. This dependence sets an obstacle for establishing a universal cutoff to distinguish clinically significant accelerated aging from normal aging. Depending on the composition of the reference population in terms of sex, race, ethnicity, socioeconomic status, and early life experiences, an individual may be determined to have accelerated aging against a socially privileged reference background but decelerated aging against a disadvantaged one. This raises serious concerns about equity, standardization, and interpretability. Without a universal reference population or robust norms across diverse groups, it becomes impossible to define consistent cutoffs that would indicate clinically meaningful deviation. Moreover, deploying reference-dependent clocks in clinical and commercial settings could inadvertently reinforce existing health inequities, pathologizing individuals for deviating from biologically privileged norms.

3.4. Unclear cost-benefit and cost-effectiveness relationships

Due to limited resources, cost-benefit and cost-effectiveness ratios of a biomarker must reach acceptable thresholds before decision makers can promote it for wider clinical applications. Although there often exist multiple methods for measuring the same biomarker, some methods may be utilized more frequently due to their low costs, even if another method is superior in terms of accuracy. For example, creatinine can be measured clinically in two ways: Jaffe (alkaline picric acid) methods and enzymatic methods. The enzymatic methods have greater specificity than Jaffe methods but have been less widely used because of their higher cost [104]. Although the cost difference between the two types of methods may be just \$1–\$2, these costs accumulate quickly, as up to 200,000 samples may be processed by a large hospital laboratory per year [105].

Currently, there is a lack of evidence supporting the idea that epigenetic clocks have cost-effectiveness or cost-benefit ratios comparable to other common clinical biomarkers. The costs of common clinical diagnostic tests such as glucose, HbA1c, total cholesterol, and creatinine are relatively low, with each item costing less than \$10 per sample [94,95,98,99,102,103,105]. Troponin assays are somewhat more costly, ranging from \$12 to \$246 [108]. In contrast, the cost of producing epigenetic clock estimates is \$240–\$512 per replicate, often with multiple replicates needed per sample [88–90]. Although high cost is not clinically prohibitive in itself, the high price must associate with robust clinical outcomes, and the incremental cost-effectiveness ratio (ICER) should exceed the willingness-to-pay (WTP) threshold. For example, genetic testing of *BRCA1*, *BRCA2*, and *PALB2* pathogenic variants for breast and ovarian cancer prevention among women aged 30 to 35 years in the U.S. was found to be more cost effective as compared with family history-based testing. The ICER of genetic testing versus family history-based testing was estimated to be \$55,548 (adjusted to 2022 US dollars) per quality-adjusted life-year (QALY) gained, which was under the WTP threshold of

\$100,000 per QALY. The input parameter of the genetic testing cost was set to \$300 in the model and sensitivity analyses indicated that when the cost exceeded \$825, such a genetic testing would not be cost-effective [123]. In addition, the cost-effectiveness determination varies by location. A cost-benefit analysis in Iran showed genetic screening was economically inferior to family history-based screening for breast cancer [124]. Similar economic analyses are scarce for epigenetic clocks. A recent study showed that caloric restriction based on DunedinPACE in adults aged 50 years and older could generate cumulative healthcare savings up to 131,608 Swiss Francs (adjusted to 2024 cost) per person across 40 years [125]. However, this estimation is limited to the intervention of caloric restriction and one epigenetic clock (DunedinPACE) and is based on the most optimistic scenario excluding costs associated with clock monitoring. Moreover, these findings are derived from population-level research and do not overcome the previously mentioned barriers associated with application of epigenetic clocks to the individual level.

4. Repercussions of adopting epigenetic clocks for monitoring individual-level health

The appeal of epigenetic clocks as tools for monitoring individual-level health lies in their apparent ability to distill complex biological information into a single quantitative measure of “biological age.” However, this reduction masks significant conceptual and technical limitations that carry substantial risks if such clocks are adopted in personalized health contexts. Much like the story of the body mass index (BMI), which is a simple measurement and broadly useful for population-level screening yet often shown to misclassify individuals (e.g., failing to distinguish lean vs. fat mass, misestimating risk in different ethnic or sex groups) [126–128], epigenetic clocks may suffer analogous limitations. Consequences of the misapplication of epigenetic clocks to monitor individuals are far-reaching: shaping clinical decisions in ways that are at best a waste of money and at worst harmful, biasing insurance or employment outcomes, and reinforcing existing health inequities.

4.1. Unnecessary and harmful medical interventions

The use of a single, aggregate epigenetic age score may lead clinicians and patients to interpret biological age acceleration as an urgent health risk, prompting action despite the absence of mechanistic clarity or validated clinical thresholds. Yet, as we outlined above, clock estimates are influenced by a wide range of transient and context-dependent technical, environmental, and biological factors. At the individual level, a single clock reading is more likely to reflect a weak and noisy signal than a reliable or interpretable marker of aging. Acting on such a signal in clinical settings risks pathologizing normal biological variation.

Furthermore, adoption of epigenetic clocks as clinical biomarkers could open the door to their use in justifying unnecessary, unproven, or even harmful interventions. In this context, clock readings may become more of a marketing

metric than a meaningful diagnostic, encouraging overmedicalization of wellness and fueling health anxiety. Application of epigenetic clocks in individual health decisions may additionally divert attention from evidence-based practices and expose patients to more harm than benefit. One reason for this risk is the lack of clarity about what changes in clock scores actually signify biologically. For example, Mitteldorf [129] has argued that while GrimAge is one of the most accurate clocks for predicting mortality, its components, such as smoking-associated CpG sites, raise interpretive challenges. He suggests that methylation differences between smokers and nonsmokers may partly reflect upregulated *repair* processes in response to smoking-induced damage. Thus, an intervention that “reverses” GrimAge may appear beneficial, but could simply be suppressing repair pathways rather than reducing biological damage. In such a case, GrimAge would reward anti-repair changes as though they were truly anti-aging, an outcome that could mislead both researchers, the public, and clinicians, thereby obscuring the need for further medical treatment. This interpretive instability becomes a critical liability when clinical actions hinge on mechanistic clarity.

Although no direct evidence exists yet to document harm from individual use of epigenetic clocks, analogous evidence from direct-to-consumer genetics and health biomarker industries strongly suggests predictable risks. Research on consumer interpretation of genetic risk measurements shows that some individuals (though not all [130]) may misinterpret probabilistic data as deterministic, especially when presented without adequate context [131]. Misunderstandings can result in unwarranted anxiety, fatalism, false reassurance, or disengagement from legitimate medical care [132,133]. Epigenetic clocks are arguably even more prone to misinterpretation than genetic markers, given their ambiguous mechanistic basis, high sensitivity to social and environmental contexts, and lack of individualized clinical thresholds. Clear communication could reduce misinterpretation and reduce harm, but currently there is little evidence that such framing consistently prevents misuse or results in long term positive change.

Although the harm that epigenetic clocks may cause is speculative, other clinical machine learning or computational-based algorithms leading to patient harm have already been well-documented. Cases in which algorithms trained with biased data (or interpreted through the lenses of structurally biased institutions) have worsened racial inequities in clinical decision making. For example, a widely used healthcare algorithm systematically underestimated the health needs of Black patients because it used healthcare costs as a proxy for health status, thus embedding structural racism with care access into a seemingly ‘objective’ tool. Similarly, racially biased glomerular filtration rate estimation formulas have influenced transplant eligibility, and race-based correction factors in obstetric risk tools have led to misallocation of care [134,135]. For epigenetic clocks, these risks are perhaps even more pertinent given that their construction is probabilistic, derived without regard for mechanism, and acutely influenced by a host of internal and external sources of variability that may have little to nothing to do with the health of an individual.

4.2. Reinforcement of structural health inequities

Even if we could overcome the inherent technical and biological variability of epigenetic clocks, and define clear clinically meaningful cutoffs, the use of such clocks risks reinforcing the very health disparities that epigenomic science aims to expose. Accelerated biological aging, as captured by most clocks, is strongly associated with early-life adversity, economic deprivation, chronic stress, and systemic discrimination [81,136]. This sensitivity makes clocks useful in population-level research but renders them ethically fraught as tools for individual clinical decision-making.

A leading concern here is “reference population” mismatch. Many clocks are calibrated using legacy datasets that disproportionately reflect white, higher-socioeconomic status populations with fewer lifetime adversities. A patient from a marginalized background or who grew up in a high-adversity environment may present as biologically “older” than their chronological age, not because of modifiable disease risk, but because of the long-lasting epigenetic imprint of unjust early or ongoing social conditions over which they have no choice or control. The appearance of “risk” here is not necessarily intrinsic to the individual’s biology, but represents a statistical artifact of misaligned context given the reference population used during clock construction. If clocks are used to guide preventive care, resource allocation, or therapeutic decision-making, the burden of structural inequity is reinscribed at the molecular level and situated as personal pathology. Positioning epigenetic clock scores as ‘neutral biomarkers’ erases the historical and sociopolitical conditions that shape them. Moreover, treating clock scores as clinical liabilities risks pathologizing lived experience, leading to higher perceived risk, or even denial of care pathways that are contingent upon more favorable baseline conditions. For instance, in the United States healthcare system, preexisting conditions have often been used to justify denial of coverage, inflated premiums, or restricted treatment options, especially prior to regulatory protections like the Affordable Care Act. If epigenetic age acceleration is interpreted similarly, as a proxy for latent disease risk at the level of an individual, it could serve as a new molecular “preexisting condition” used to drive health inequity. The concern here is mission drift: epigenetic clocks, originally developed to understand how the social environment becomes biologically embedded, risk being deployed in ways that individualize risk and erase context. Their incorporation into clinical decision-making, however well-intentioned, threatens to deepen existing inequities, not resolve them.

4.3. Misuse in non-clinical contexts

The application of epigenetic clocks outside of healthcare, particularly in insurance underwriting and employment decision-making, poses a fundamental ethical and scientific problem [137]. Despite the lack of consensus on interpretation, clocks are already migrating into commercial use; this scenario is not hypothetical [138]. In 2023, FOXO Technologies acquired exclusive rights to GrimAge and PhenoAge from UCLA and began integrating these metrics into life insurance underwriting algorithms, claiming to assess long-term

mortality risk using saliva samples. Such applications are being pursued in the absence of robust standards for interpretation, validation across diverse populations, or regulatory oversight.

Even if the use of these clocks was initially restricted to clinical settings, there is little historical precedent for keeping powerful biological metrics siloed. BMI, polygenic risk scores, and even blood pressure have all been co-opted by industries seeking to quantify individual health risk and push financial liability onto consumers. There is no reason to believe epigenetic clocks will be treated differently, particularly as their molecular authority is marketed as cutting-edge precision.

This misuse is especially concerning because clocks are not neutral or purely biological metrics; they likely reflect cumulative exposure to environmental, social, and economic factors over time. When used to guide pricing or eligibility decisions in a marketplace, they become tools of stratification, penalizing individuals for biologically embedded life circumstances beyond their control rather than health behaviors [139]. In these domains, clocks are *categorically inappropriate*, functioning as proxies for lived inequality rather than fair assessments of health behaviors.

5. Future perspectives

We have argued that there are substantial technological and biological barriers that prohibit current epigenetic clocks from being useful on an individual level. These barriers result in epigenetic clocks not performing well on clinically relevant criteria when compared to contemporary clinical tests. We have also argued that implementation of current epigenetic clocks at an individual level may lead to harmful societal and personal consequences. However, would epigenetic clocks be individually useful if all these barriers were able to be overcome?

We believe that in a future day, even if all technical and biological barriers were overcome, the current conceptualization of epigenetic clocks would remain uninformative on a personal level. The broadness of factors that can contribute to transient accelerated epigenetic aging prohibits any useful clinical or personal interpretations of clock results. While alternative DNAm-based algorithms for predicting specific health outcomes (such as specific lymphomas, Alzheimer’s disease, etc.) may become useful, we argue that these algorithms would be fundamentally different in purpose and scope than current epigenetic clocks, which generally aim to capture overall features of complex and multifaceted biological aging processes.

Even when the purpose is narrowly defined (such as is the case in first-generation clocks that predict chronological age), most existing clocks still lack the conceptual specificity, biological interpretability, and validation frameworks necessary for individual-level decision-making. A clock trained to predict mortality risk, such as GrimAge, provides probabilistic information derived from group-level associations, not mechanistic insight into why a particular individual’s score is elevated, or which pathways may be driving that signal. This probabilistic nature is scientifically appropriate for population-level research but problematic when applied to an individual. A “high risk” clock reading cannot

distinguish between transient exposures, reversible physiological states, or durable biological changes, and it cannot specify what type of intervention would meaningfully alter the trajectory. While there are biomarkers with a probabilistic basis that have made the jump from population research to clinical utility (e.g., polygenic risk scores, Framingham risk scores, etc.) these markers are typically accompanied by a more direct mechanistic linkage to the endpoint on which they inform. Yet, these tools suffer from some of the same limitations inherent to epigenetic clocks, such as population stratification, poor generalizability across ancestries, and risks of misinterpretation.

Epigenetic clocks, by comparison, present even greater challenges to clinical translation. Clocks trained on specific endpoints in particular tissues are derived from reference populations whose demographic, social, and environmental characteristics shape the model parameters. Thus, a clock is valid for detecting relative differences in a population, but clinical translation to individuals from a multitude of differing contexts remains confounded. The issue, as we see it, is that the heterogeneity of clocks, combined with their statistical (rather than mechanistic) basis, makes individual-level interpretation untenable. Without clear biological anchors, actionable thresholds, and validation across contexts, clocks risk being misapplied and misused at the level of the individual.

The power of epigenetic clocks lies in population-level research, where they can illuminate how environments, policies, and life-course exposures shape aging biology. Their technical and biological sensitivity to context, their technical variability, and their entanglement with structural exposures make epigenetic clocks unfit for assigning personal risk or responsibility. Any tool that links opportunity or cost to a metric so closely tied to social inequality must be approached with suspicion, not celebration [140]. If we value the promise of epigenetic science, we must also respect its limits. Clocks are valuable, but only when used in ways that match their design, their strengths, and their scientific maturity.

Author contributions

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Disclosure statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This manuscript is the result of funding in whole or in part by the National Institutes of Health (NIH). This work was supported by the National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases [R01DK139357], and National Institute of Nursing Research [R01NR021020] and [R01NR019610]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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