Challenges and recommendations for the translation of biomarkers of aging

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Biomarkers of aging (BOA) are quantitative parameters that predict biological age and ideally its changes in response to interventions. In recent years, many promising molecular and omic BOA have emerged with an enormous potential for translational geroscience and improving healthspan. However, clinical translation remains limited, in part due to the gap between preclinical research and the application of BOA in clinical research and other translational settings. We surveyed experts in these areas to better understand current challenges for the translation of aging biomarkers. We identified six key barriers to clinical translation and developed guidance for the field to overcome them. Core recommendations include linking BOA to clinically actionable insights, improving affordability and availability to broad populations and validation of biomarkers that are robust and responsive at the level of individuals. Our work provides key insights and practical recommendations to overcome barriers impeding clinical translation of BOA.

Translational geroscience posits that targeting aging can delay or prevent multiple chronic diseases[1] and may unlock promising improvements in healthspan. BOA are quantitative parameters that either alone or in a composite predict biological age (that is, 'an individual's age defined by the level of age-dependent biological changes, such as molecular and cellular damage accumulation and ideally its changes in response to interventions' (ref. 2)). Although such biomarkers were first proposed decades ago[3], recent omic advances have amplified research activity and identified many promising candidates[2]. However, these revolutionary tools remain largely within the realms of preclinical and observational research. Application of BOA for both clinical research and routine implementation (including decision making) remains minimal, partially due to limited coordination in the aging field.

The Biomarkers of Aging Consortium (https://www.agingconsortium.org) was formed to enhance collaboration across the field. We recently provided consensus on key working terminology and use cases[2], and reviewed biomarker validation studies, providing guidelines to improve future validation efforts for robust comparison of

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BOA[4]. Although previous work has formalized challenges and opportunities for DNA methylation aging clocks[5,6], a general roadmap for clinical translation of BOA encompassing data modalities beyond DNA methylation remains an unmet need.

We questioned a panel of experts participating in the 2023 Biomarkers of Aging Symposium to identify key challenges hampering translation of BOA for use in human clinical research and routine implementation and to formulate strategies on how to overcome them. Our goal in synthesizing these expert opinions is to provide forward-facing action items to accelerate the clinical translation of BOA. Moreover, we hope to initiate a necessary conversation and foster enhanced collaboration between preclinical and clinical experts that will be vital for the future optimization and application of BOA.

Data sharing for biomarker development and validation (challenge 1)

Background

Thorough validation across diverse human populations consistently emerged as a critical need to enable the clinical translation of BOA. Independent validation depends on large, high-quality datasets, necessitating data sharing. Various regulatory frameworks have been established to improve open science and data sharing. For instance, the European Research Council mandates open access to publications from their funded projects and strongly embraces the FAIR (findable, accessible, interoperable and reusable)[7] Data Principles[8]. However, legal barriers persist, such as the European Union (EU) General Data Protection Regulation (GDPR) act, which tightly governs the processing and transfer of personal data of EU citizens, and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule and the Federal Policy for Protection of Human Subjects (Common Rule) in the USA[9]. Respondents commented on data sharing and annotation and how both could be improved.

Challenge

Responses indicated various reasons why researchers prefer not to share data. These included substantial time and effort required to ensure compliance with FAIR principles (10 of 29 respondents) in exchange for little to no professional reward, desire to publish novel results and considerations surrounding intellectual property, which are particularly relevant for potentially patentable tools such as biomarkers (2 of 29 respondents) or subtleties in the data that could be overlooked by outside analysts and lead to spurious results, for which the data-generating group does not want to be responsible (1 of 29 respondents). Moreover, although critically needed for biomarker research and translation, data from human participants can be difficult to share due to structural and legal barriers, including EU GDPR and US laws that can be restrictive, vague and overall challenging for researchers to navigate, as noted by several respondents. For instance, in the USA, neither the Health Insurance Portability and Accountability Act nor the Common Rule were tailored toward biobanks[9]. Although efforts to enable data sharing under GDPR and similar legal frameworks exist[10,11], as do commendable examples of large organizations or biobanks managing efficient access, such as UK Biobank[12], the All of Us Research Hub[13] (https://www.researchallofus.org), the Veterans Affairs Open Data Portal (https://www.data.va.gov/) and the China Kadoori Biobank[14] (https://www.ckbiobank.org/), there are no clear guidelines for researchers on how to share data from human participants, in particular across different legal systems.

Overall, our respondents indicated that the current situation leaves whether, and to what extent, data are openly shared up to individual researchers who often lack the required legal expertise. Occasionally, the combination of barriers and limited incentive may lead to instances in which data are shared only 'in principle', for example, providing access to raw data but not metadata such as study protocols, standard operating procedures and other information, effectively rendering reuse impossible. Altogether, the responses of our panel suggest that the status quo of data sharing hampers systematic biomarker validation and clinical translation.

Recommendations

Our respondents pointed to both incentives ('carrot'; preferred) for researchers who adhere to the FAIR Principles and penalties ('stick') for those who do not:

Carrot. Many respondents highlighted the importance of normalizing the practice of data sharing through positive reinforcement and leading by example. Over a third (13 of 29) of respondents suggested that tangible support or rewards would incentivize this process and ensure better data quality: for instance, funding agencies may consider grant opportunities for data curation, documentation, sharing and harmonization, alongside long-term financial support for personnel to ensure continuity. Additionally, contributions of data creators should be given more weight, for instance, via citations, as metrics on a researcher's CV, considerations for promotion at academic institutions and key performance indicators of universities. Extra effort to achieve this goal should, however, not lead to unreasonable burdens that excessively interfere with the primary research responsibilities of investigators.

Stick. Some respondents suggested more punitive approaches for (repeatedly) failing to share data, indicating that existing systems only achieve 'minimum compliance, often with long delays' and that regulatory and funding bodies overseeing research should both reward data sharing and penalize existing data holders not providing reasonable access to (publicly funded) data. Potential penalization could go as far as imposing consequences for noncompliance with data sharing similar to those for research misconduct (see, for example, https://ori.hhs.gov/content/case_summary) or tying access to future funding opportunities to data-sharing compliance and data usefulness, with progress reports to funders requiring information on tangible access to datasets generated. One respondent mentioned that scientific journals can also have a key role, flagging data-sharing noncompliance with expressions of concern, with possible escalation to study retraction. Funding agencies could require publications in journals to adhere to rigorous data-sharing policies for all funded studies; similar approaches ensure open access of publicly funded research (for example, the NIH Open Access Policy, https://publicaccess.nih.gov/policy.htm; European Research Council Open Access guidelines, https://erc.europa.eu/manage-your-project/open-science).

Improving data-sharing infrastructure. Many respondents urged the need for changes in research culture and legal frameworks to improve data sharing and ultimately support the translation of BOA, while noting that sharing of human data must include appropriate protections for participants. This also relates to issues with consent: some of the most valuable data are derived from longitudinal studies initiated at a time when data sharing was less common, and many informed consent forms included limits to data sharing, although some have been updated since then. Future efforts between the wider medical research community and legal entities should initiate a discussion on how to overcome these limitations. Advocacy groups such as the Alliance for Longevity Initiatives (https://a4li.org/) may be particularly helpful in these efforts. In practice, overcoming issues with data sharing while ensuring appropriate protection for human participants may be accomplished by:

1. **Enhanced support from funding organizations**. This includes support for preparing and linking data with FAIR datahubs and providing training and software options for effective and safe data-request procedures in ways that are interoperable from the outset.

Table 1 | Arguments for or against the inclusion of eight main evaluation criteria for BOA

Criterion	Arguments for	Arguments against
Correlates with chronological age	Biomarkers that do not change with chronological age are by definition not indicative of aging.	Aging trajectories differ for each individual, and biomarkers with weak correlations with chronological age can still be useful to distinguish differences in biological age within cohorts of equal chronological age. Paradoxically, as the correlation with chronological age increases, the information of the biomarker beyond age decreases. Biomarkers of the rate of aging may moreover have the potential to indicate increased longevity without a correlation with chronological age[44]. Successful geroprotectors may also upregulate protective or adaptive anti-aging pathways that could correlate positively with chronological age.
Predicts all-cause mortality/survival	BOA should reflect the increased risk of all-cause mortality associated with increased biological age.	The effects of age-related damage accumulation on mortality only become apparent in geriatric populations. Accelerated aging in younger populations can still cause more subtle health problems that can be detected with BOA.
Predicts frailty and/or healthspan	BOA should reflect the increased frailty and decreased healthspan associated with increased biological age.	The effects of age-related damage accumulation on frailty and healthspan only become apparent in geriatric populations. Accelerated aging in younger populations can still cause more subtle health problems that can be detected with BOA.
Predicts incidence of multiple age-related diseases	Aging is a systemic process and increases the risk of a plethora of diseases simultaneously. If a biomarker only predicts the risk of a handful of diseases, it is not measuring aging.	Aging can be accelerated in specific organs or systems[45]. Biomarkers that predict specific age-related diseases are still useful in clinical practice.
Reflects causal aspects of aging	Biomarkers built on causal features help to improve biological understanding of aging and reliably measure the effects of anti-aging interventions.	Useful biomarkers can be built without detailed causal understanding. Causality can also be evaluated post hoc.
Responds to factors that accelerate aging	Factors such as smoking increase the risk of various age-related diseases and all-cause mortality and may influence aging trajectories. Response to these exposures allows for the assessment of differences in biological age for individuals of equal chronological age.	Factors such as smoking, UV exposure and so on only mimic aspects of aging. Biological response to these factors may not be relevant to assess the effects of anti-aging interventions.
Responds to putative geroprotectors	BOA that do not capture the effects of geroprotectors on healthspan and lifespan do not measure changes in biological age and are useless to assess the effects of new putative anti-aging interventions.	No existing geroprotectors have been validated in humans. This may lead to a circularity argument, in which biomarkers are developed using changes induced by putative interventions and thus 'validate' these interventions but do not necessarily truly capture a geroprotective effect.
Validated in diverse populations	BOA need to be widely applicable to ensure that they capture universal aspects of aging and can be reliably applied to every patient.	Many biomarkers only work for specific species or tissues. Biomarkers that are only valid in a specific population can still be highly useful for that population.

2. **Establishment of federated portals and knowledge bases**. These repositories would house data behind firewalls but allow for visualization and queries, contingent on data-use agreements, and would be widely accessible. Federated data portals may be particularly useful for large-scale studies for which it is not feasible, for practical or privacy reasons, to deposit data in centralized repositories and could be built on models such as those used by UK Biobank[12], the All of Us Research Hub (https://researchallofus.org/), the Veterans Affairs Open Data Portal (https://www.data.va.gov/) or the GTEx Consortium[15]. Such platforms would be enabled by standardized data formats and architecture and distributed computing to reduce the cost of data migration and conversion and enhance the quality and interoperability of data, facilitating replication and meta-analysis. Such data portals may improve data harmonization and comparability, and – in combination with other tools to help to standardize measurements – transform our field's ability to link biomarkers and outcomes. Notable tools for standardization include the NIH's PhenX Toolkit (https://www.phenxtoolkit.org), which provides a resource of standardized protocols for various research areas, and frameworks proposed by the NIA Translational Geroscience Network[16], which aims to optimize resource utilization and promote the development of shared protocols and outcome measures.
3. **Promotion of best practices and lobbying by the Biomarkers of Aging Consortium**. The consortium should propose and widely promote minimal criteria on what data and sampling are necessary to bring BOA to the clinic, identify studies and resources (for example, biobanks) that already have valuable data for such purposes and lobby governments and funding bodies to ensure that the data are shared freely without barriers.
4. **Provide credit to researchers by tracking metrics for data sharing**. Datasets and databases generated by data providers can be assigned tracking numbers and digital object identifiers that can be cited in publications by the data providers and those who reuse the data.

Relative importance of criteria for BOA (challenge 2)

Background

An objective framework is needed to evaluate the feasibility of clinical translation of new candidate BOA. Our recent work outlined key evaluation criteria for BOA[2]: feasibility, validity, mechanism, generalizability, responsiveness and cost. Although establishing consensus terminology and a framework for BOA classification built on existing regulatory guidelines marked substantial progress in the field, previous work did not assess the relative importance of these criteria. Here, we included eight main criteria to assess the effectiveness of BOA and provide arguments for or against including these criteria, which may be dependent on the application and target population, in Table 1. We leveraged the combined expertise of our respondents to assess the relative importance of these criteria for biomarker translation, primarily focusing on their application in human clinical studies.

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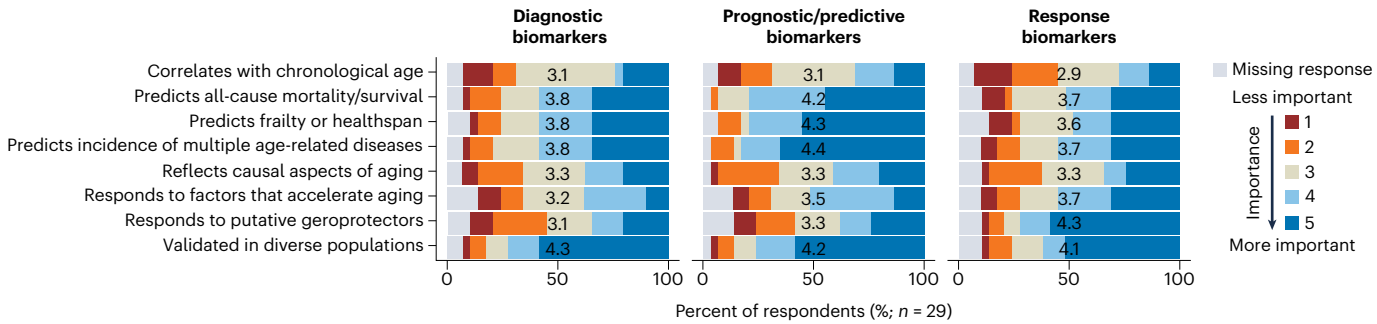

Fig. 1 | Ranking of biomarker criteria. Percentages of respondents who graded different criteria for diagnostic, prognostic–predictive and response BOA on a scale from 1 (not important at all) to 5 (extremely important). The mean score is shown for each category. Missing responses are colored gray. *n* = 29 of 34 invited participants completed the questionnaire.

Challenge

Our questionnaire revealed a range of opinions relating to the relative importance of evaluation criteria for BOA (Fig. 1). Although some rankings were expected and fairly common for certain biomarker classes, such as high importance ascribed to the ability of predictive biomarkers to predict multiple age-related diseases or responsiveness to putative geroprotectors for response biomarkers, there was a strong divergence of opinions around other criteria, such as the importance of correlation between BOA and chronological age and the need for biomarkers to reflect causal aspects of aging. Some respondents indicated that mechanistically informed BOA are essential, as otherwise the biomarker is not measuring the aging process. Other responses reflected a more pragmatic approach and proposed that, if the biomarker has been validated appropriately and responds to biological age-modulating interventions, true causality is not an absolute necessity. Some of these respondents nevertheless highlighted potential missed opportunities of failing to understand the links to the biology of aging, even if it occurs post hoc. For instance, suppose a biomarker without clear links to aging mechanisms indicates an improvement of health after a particular intervention: if it is unknown what specific pathways or processes this biomarker detects within the complex backdrop of an aging system in which many disease processes co-occur, the biomarker's use cases for future studies may be unclear. Another respondent highlighted a general challenge: 'we have yet to figure out which biological pathways are shared by which co-existing chronic conditions'.

Aside from the critical importance of cross-population validation, our respondents indicated that the second most important criterion across various types of BOA is the ability to predict the incidence of multiple aging-associated diseases. Interestingly, prediction of age-related diseases ranked higher than prediction of frailty, all-cause mortality, survival and healthspan, possibly because there is not yet a universally agreed-upon definition of healthspan.

Recommendations

Our results underscore the challenge in building consensus on prioritization of specific BOA. This is problematic, as expert consensus is an important component of regulatory biomarker qualification, and recognizing the most important features of a biomarker remains a key step for its clinical translation. Moreover, we feel that working toward a broad consensus will be essential for the coordinated advancement and translation of BOA. We expect that further Delphi-based consensus building, which we have shown to be effective and productive in this field[2,4], will be needed to define criteria for different types and applications of biomarkers (for example, diagnostic, predictive or response). Importantly, such consensus-building efforts must also include clinicians and other end users.

Validation across diverse populations is clearly of high importance. This aligns with our recent work that identified systematic cross-population validation as one of the key unmet needs to advance BOA[4] and recognizes the importance of scaling up validation and benchmarking efforts of multiple BOA across multiple cohorts. Such efforts have the potential to clarify the relative importance of the evaluation criteria discussed above in a 'real-world' setting. Biolearn, a recently developed open-source library for BOA, offers an example of a platform aimed at catalyzing these critically needed validation efforts[17]. Looking further ahead, essential steps will also include post-marketing validation of BOA in randomized controlled trials and clinical studies to assess their clinical utility.

Lastly, although causality was deemed highly important by only about half of the respondents, collecting data from the clinical application of causal biomarkers offers a unique opportunity to better understand the biology of aging, which is paramount for further translatable discoveries. Moreover, understanding mechanisms underlying predictive and response properties may be important to evaluate biomarker properties and whether a change in their value truly corresponds to a change in the desired outcome. Ideally, a response biomarker should also capture possible differential responses to characteristics such as sex. Causality and a link to changes in how a patient 'feels, functions, and survives' are also critical for the establishment of validated surrogate endpoint biomarkers[18].

Age range for applications of BOA (challenge 3)

Background

Although some recent studies show that organismal aging may begin before birth[19–21], there is no consensus on the exact starting point of 'aging', and opinions run the gamut from before or at birth to later in life[19]. While the association between some BOA and chronological age is not linear (for example, DNA methylation[5]), several BOA remain somewhat associated with chronological and biological age across wide age ranges. However, it is currently unknown when during the life course aging can or should be targeted. We asked our participants which age ranges they deemed appropriate for application of BOA in human populations.

Challenge

In addition to the fundamental question of when aging begins, it is currently not clear at what chronological age ranges BOA could prove useful in a translational setting, for instance, to monitor biological aging or predict aging outcomes. It is important to note that many of our respondents were preclinical scientists, who, in considering their responses, may have placed more emphasis on the basic biological questions rather than more practical clinical considerations. Interestingly, even within this group, we found that opinions varied strongly, reflecting the general lack of consensus on many fundamental features of aging biology[2]. Approximately half of our participants felt that BOA could or should be applied from (or before) birth, and half indicated

that they would be useful from reproductive maturity (adulthood) or later in life (middle age onward).

Some participants noted that 'pan-age' biomarkers that are informative across all chronological age ranges could be used to track deviations from healthy aging trajectories throughout life. Conversely, others mentioned there is no evidence that measuring BOA in individuals before adulthood provides any information that is more valuable than the traditional measures of development to predict outcomes and trigger interventions. According to these respondents, measuring BOA in young individuals is merely an academic curiosity aimed at better understanding the biological changes that happen during development. Yet others noted that, although BOA could be used throughout life, different age ranges might require age range-specific biomarkers. The dichotomy in our responses is also mirrored more broadly by the conceptual divide between 'lumpers' and 'splitters', noted by S.H. during the 2023 Biomarkers of Aging Symposium: whereas 'lumpers' aim to identify universal, pan-tissue or even multi-species BOA, 'splitters' are more focused on specific biomarkers for given cell types, organisms or age groups.

Recommendations

Although further research is needed to validate the beginning of organismal aging, BOA may be capable of measuring biological age or the aging process across the lifespan, with the caveat that it might be more difficult to distinguish aging from development before adulthood. Intriguingly, we found that the reasons for indicating the earliest chronological age at which a biomarker can be useful to detect accelerated aging were not always intrinsically related to a respondent's belief as to when aging begins. For instance, some respondents recognized the fact that BOA may be capable of tracking biological ages across the lifespan but noted that deviations from aging trajectories may be less pronounced or important at younger ages and therefore recommended using BOA only later in life. Such responses, in which practical considerations were balanced against fundamental features of aging biology, also emerged within the other challenges (see, for example, challenge 4).

The ideal age to apply a biomarker of aging might also depend on its intended use. For example, biomarkers for prevention of aging-associated disease or dysfunction will probably be tailored toward currently healthy participants who are younger on average, whereas biomarkers that aim to assess ongoing age-related (multi)-morbidities might have more practical applications in older cohorts. Indeed, although many BOA are tailored toward prevention, geriatric patients could also benefit from BOA when used in clinical decision making.

Further research should assess and validate diverse biomarkers throughout the entire lifespan and evaluate whether universal or age-specific biomarkers may best reflect relevant clinical outcomes and indeed the underlying biology, if the rate of aging is variable over the lifespan. Importantly, biomarkers should help to identify actionable insights for various age groups that can help to guide personal prevention and longevity interventions. The decision on when and to whom BOA will be applied in the clinic will ultimately rest with clinicians, and thus better alignment between clinicians and basic scientists is necessary. This will be essential in striking a balance between the fundamental biology of aging and clinical implications of such knowledge.

Minimal criteria for clinical use and implementation (challenge 4)

Background

To successfully translate BOA, a set of minimal criteria must be met. Our previous work[2], built on seminal papers[3,22], outlined a framework for criteria to evaluate BOA for various use cases. Through this framework, we assessed the opinions of our expert respondents on the minimal criteria for BOA usage in clinical settings.

Challenge

Our questionnaire revealed recurring minimal criteria emphasized by most or all respondents. These themes included sufficient scientific evidence for a link with the outcome, reliability of biomarker measurement and assay, and biomarker availability. Accessibility to laboratories or providers for running tests, cost and financial reimbursement for biomarker measurement costs were also important concerns. Apart from these central points, diverse opinions emerged on priority criteria for specific biomarkers (Fig. 1) and use cases. Such criteria included the biomarker's ability to outperform the current standard of care, to provide information to supplement established risk factors (for example, chronological age, sex, disease burden and other epidemiological risk factors) and to guide clear clinical actions.

Recommendations

Our questionnaire responses highlighted the importance of scientific and practical considerations for minimal BOA criteria. Although criteria may vary for specific use cases, we identified a set of core criteria for clinical implementation based on our expert questionnaire. First, BOA should be easily measurable and not prohibitively expensive, which is crucial when guiding cost-effectiveness evaluations for healthcare implementations. BOA should also outperform or usefully complement the current standard of care. For instance, if the standard of care is to stratify participants by chronological age, stratification by biomarker-assessed biological age should result in a substantial enrichment of participants at risk for age-related disease compared to using chronological age alone, although it is important to note that the standard of care often includes additional disease-specific risk indicators (for example, physiological or blood-based measurements, such as the American Heart Association's Predicting Risk of Cardiovascular Disease Events (PREVENT) score[23]). To facilitate biomarker measurements in broad populations, we need programs to make these biomarkers more affordable, available and reliable as well as technical and computational methods to achieve this goal. Ultimately, given low cost and high availability, BOA could be used in a similar manner as existing risk stratification measures such as blood pressure measurement.

BOA should also fulfill established practical criteria (for example, those described in refs. 2,18), including clinical utility for a given use case. This includes a clear link to measurable outcomes and the potential to change treatment decisions to improve outcomes. However, demonstrating clinical utility requires lengthy studies. We must therefore continuously foster collaboration between biomarker developers and clinicians to gather the required evidence from routine patient visits or human clinical trials. Beyond these straightforward recommendations, many of which reflect accepted basic requirements for any biomarker, our results indicate that further steps are necessary to establish minimal clinical criteria for BOA. These more-complex issues require close collaboration across diverse areas of expertise. A priority for the BOA field (and our consortium) is fostering cross-fertilization between researchers, clinicians, regulatory bodies and funders to enable these steps. Key focus areas that we identified are (Fig. 2):

1. **Enhanced communication between BOA researchers and/or developers and clinicians**. BOA should ideally address clinical needs; yet input from clinicians is not universally prioritized by biomarker developers. For instance, in a translational setting, BOA could be created or at least optimized toward specific use cases with practical clinical applications[24]. Projects should ideally include bioinformaticians, epidemiologists and/or basic biologists. They may also involve technology companies developing biomarker measurements to ensure platform continuity, technology improvement, cost efficiency and coverage of the most relevant features.

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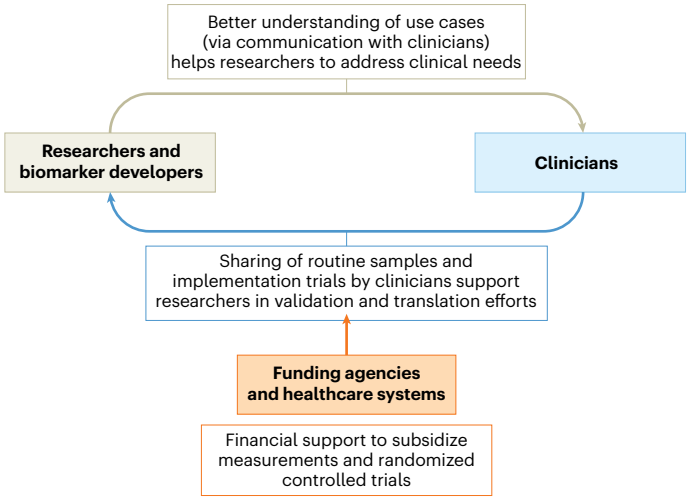

Fig. 2 | Proposed workflow for improved collaboration between researchers and biomarker developers, clinicians and funding agencies to accelerate clinical translation of BOA. Close interaction of researchers and biomarker developers with clinicians can help to address clinical needs (for example, specific or optimized biomarkers), and sharing of routine samples by clinicians can help researchers to validate and translate their findings. These interactions will ultimately need to be facilitated by a permissive environment and sufficient funding to perform biomarker profiling.

2. **Funding systems for biomarker measurements.** Increased researcher–clinician interaction could facilitate routine sample collections, substantially advancing our understanding of BOA performance across various populations. This requires direct funding or subsidizing mechanisms for such measurements. Moreover, increased funding is needed for implementation studies[25] that facilitate researcher–clinician interaction, address clinical implementation challenges and assess clinical utility.

Positioning of BOA in the current disease-specific healthcare setting (challenge 5)

Background

BOA have considerable translational potential. A particularly appealing prospect is their application in translational geroscience to identify individuals who could benefit from longevity interventions and monitor the efficacy of such interventions in preventing several age-related diseases[1]. A general paradigmatic shift to more proactive and preventative healthcare has been proposed, termed 'P4 medicine' (proactive, preventive, predictive, personalized[26]), that may ultimately optimize health but has not yet been fully implemented in most systems. We asked respondents how they think BOA may fit in current or future healthcare systems, initially for clinical research and ultimately for routine implementation (Fig. 3b).

Challenge

A key challenge for BOA translation is their positioning in current healthcare systems, which primarily focus on treating diseases or conditions after they appear[27], although some successful examples of pre-disease detection exist that avoid disease exacerbation via targeted intervention: these include hypertension (measured via blood pressure) to avoid heart attacks and heart failure, hyperglycemia (measured via test strips) to avoid diabetes, osteoporosis (measured through bone density) to avoid bone fractures and others. Primary care providers are not likely to adopt BOA as routine clinical tools until they are thoroughly validated and become integrated into the standard of care. Although some BOA can predict all-cause mortality and multi-morbidity (for example, GrimAge[28]), there is currently no blueprint on what clinical action could or should be taken in response to an aberrant BOA result or how to integrate such findings into clinical care. Moreover, many countries have not yet sufficiently established financial structures to facilitate effective preventive medicine (for example, the USA[27]), such as supporting individuals to take control of their own health through preventative tests, active health monitoring and reimbursement for health-promoting interventions. Below 3% of US healthcare spending is allocated to preventative medicine (according to the Organisation for Economic Co-operation and Development, https://stats.oecd.org/Index.aspx?DataSetCode=SHA#). Interestingly, low-income countries spend proportionally larger amounts on preventative medicine[29]. Along with a broad paradigmatic shift toward preventative medicine, a roadmap for clinical implementation of BOA is needed to leverage their full potential.

Recommendations

Respondents highlighted that BOA are invaluable instruments in promoting the shift toward pro-longevity and preventative medicine. However, more readily attainable opportunities that complement existing medical approaches were also identified. Although the recommendations below do not constitute regulatory guidance, they provide an outlook on the potential trajectory of BOA to the clinic (Fig. 3b).

One immediate potential clinical use of BOA is for patient or participant stratification in clinical research, such as tailoring participant follow-up intervals or making treatment decisions based on BOA results, in parallel with other precision medicine approaches for participant screening and risk stratification (for example, breast cancer risk prediction models[30]). Individuals with aberrant BOA results may benefit from further or more frequent testing for certain diseases, enabling more efficient allocation of healthcare resources. Currently, several healthcare programs define screening or treatment cutoffs based on chronological age that may be outperformed by BOA. For instance, BOA have been shown to outperform chronological age for estimating future hospital admissions[31]. BOA may also be helpful in situations not directly related to aging-associated diseases, such as the prediction of outcomes to (planned) stressors (for example, surgery[32], chemotherapy[33], mental disease[34], psychosocial stress[35,36] and pollution[37]). For these and other applications below, there is a need for new International Classification of Diseases codes that classify accelerated biological aging, extending beyond the existing codes (XT9T category)[38]. Such approaches will require close cooperation between biomarker developers, clinicians and medical regulatory bodies to establish consensus. Additionally, it will be critical to establish whether processes captured by BOA are reflected in multiple age-related conditions and to identify the conditions for which biomarkers are informative. It is important to note that the true value of BOA will lie in their potential ability to complement or even outperform risk prediction based on chronological age and the sum of disease-specific indicators and risk biomarkers (for example, blood pressure, cholesterol and others).

BOA may also be useful to assess responses to treatments or preventative efforts, for instance, by repeatedly monitoring biomarker levels over the course of treatment and linking these changes to clinical outcomes. Clinical trials testing effectiveness of interventions are typically evaluated based on the overall or average effect, but often a substantial proportion of participants are either 'nonresponders' or, in the worst case, actively harmed by the intervention[39]. BOA could help to identify (non)responders, and further characterization of (non) responders may help to better understand reasons for response (or lack thereof) to ultimately realize some of the potential of precision medicine. Such approaches could be advanced by systematic investigation with affordable biomarkers applied to consecutive series of patients entering a clinic, identifying clusters of patients based on biomarker readouts. Importantly, evidence gathered from existing

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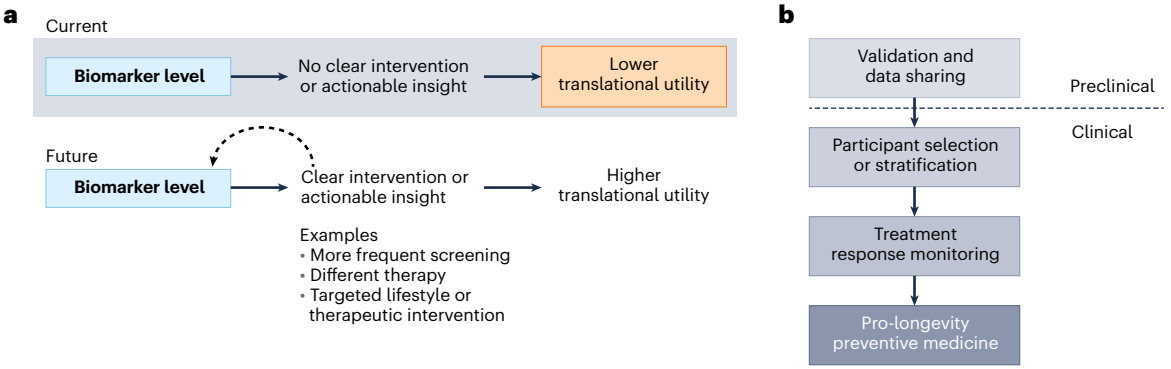

Fig. 3 | Connection of biomarkers to clinical insights and proposed steps for their translational use. a, Currently, many BOA are not clearly linked to an actionable insight beyond general health-promoting interventions and may provide lower translational utility for guiding individual healthcare. A key step for future research in BOA will be to link their levels to actionable insights for healthcare. Clinical research could explore whether biomarker levels may enable more targeted screening, different therapies for existing diseases or targeted lifestyle or therapeutic interventions for optimizing health, maximizing the translational utility of a biomarker. **b**, Successful translation of BOA may use a stepwise approach, building on solid validation (dependent on data sharing). Clinical use can initially be in research settings for participant selection or stratification (for example, to select participants or patients for healthcare screening or intervention based on biological age rather than chronological age). With emerging evidence and better knowledge about individual actionable insights, biomarkers can be leveraged for treatment response monitoring. Ultimately, biomarkers should be part of a paradigm shift in medicine toward optimizing health.

early-stage clinical implementation efforts can be used to qualify BOA as validated surrogate endpoint biomarkers that are clearly linked to clinical outcomes and can be used as endpoints in clinical trials[4]. These steps will require robust implementation science frameworks[25], including randomized controlled trials, to study the efficacy and usefulness of BOA for specific purposes. For example, biomarkers could be linked to other existing and known endpoints and interventions, such as blood pressure and antihypertensives: blood pressure correlates with age and predicts multiple age-related outcomes including mortality and its targeted normalization can reduce disease risk and mortality. Assessment of BOAs in conjunction with measurement of the known surrogate endpoint biomarker of blood pressure in patients taking antihypertensives may provide a useful reference by which less well-understood biomarkers and interventions could be evaluated.

Ultimately, to fully realize the potential of BOA, a paradigm shift in medicine is required, in which the current focus on specific diseases should shift toward maintaining function and intrinsic capacities in an aging society[26]. Because BOA aim to quantify aging rather than specific diseases, they will be essential tools to predict aging-related functional decline. In the long term, systems that prioritize 'healthcare versus sick care' and integrative (whole-body) health may both decrease healthcare costs and improve overall population health by reducing the incidence of many age-related diseases simultaneously. However, this paradigm shift will require large upfront financial investments. For instance, health services and insurance companies will need to begin covering the cost of BOA testing. Advances in digital health and artificial intelligence that provide opportunities for individual prediction of age-related morbidity and modeling the effect of interventions, such as via 'digital twins' or 'virtual twins' (refs. 40,41), may offset this cost as these technologies progress. For instance, one respondent proposed that a digital twin could be used to simulate the effect of longevity interventions or other lifestyle factors on health and appearance over several decades. More broadly speaking, advances in digital BOA obtained via wearable devices or imaging[2] capable of capturing detailed longitudinal trajectories, alone or in combination with molecular biomarkers, and the application of artificial intelligence for data exploration and interpretation will probably provide notable advantages for monitoring age-related functional decline. We note that although a move toward maximizing healthspan in currently healthy individuals is essential[42], improving health and targeting already existing diseases in aging populations is an equally important goal.

Connecting BOA with actionable insights in healthcare and preventative settings (challenge 6)

Background

Although BOA have not yet been broadly adopted in routine clinical settings, several biomarkers are already available for health monitoring, mostly on a self-pay basis. To understand the level of maturity and acceptance of existing BOA for individual health monitoring, we assessed how many of our experts use or would consider using BOA to monitor their own health. Approximately 40% of respondents confirmed tracking their own health with BOA.

Challenge

Respondents that did not personally use BOA cited (1) a caution over individual predictiveness ('we are not there yet'), (2) being in good health and (3) that it is currently not clear how the information generated by a biomarker of aging could provide actionable insights. Although some interventions such as a healthy diet and regular exercise are generally useful regardless of biological age, there are currently few defined medical indications or contraindications for the use of pharmacological geroprotective interventions in response to aging biomarker results. For instance, age-related changes in blood lipid levels may potentially be addressed by supplementation or medications that target this specific feature. However, far fewer comparable interventions have been shown to directly affect other BOA, such as epigenetic clocks. This lack of links to actionable insights based on the results of existing BOA was also reflected in the responses of participants who track their own health status over time. Most of these respondents used classic clinical metrics (for example, blood biochemistry, inflammatory markers or body composition) that correlate with chronological age to track their own health but would like to see more actionable insights before starting to use more integrative BOA.

Ultimately, a successful biomarker of aging should represent a meaningful measure of an individual's health status, including their quality of life, that can be leveraged by an individual or their healthcare professionals to identify actionable changes (for example, recommending a certain geroprotector or other health improvements or even alerting an individual to urgently visit the emergency room).

This challenge is not trivial: for example, neurodegeneration is highly complex to detect, especially before the onset of symptoms, but its accurate, timely detection is highly relevant to guide a patient's future healthcare.

Several respondents also mentioned challenges in accessibility and cost. Indeed, many current BOA are frequently used in academic settings (for example, epigenetic or transcriptomic clocks) but are not yet suited for high-throughput analysis, as they are prohibitively expensive. Conversely, biomarkers such as blood chemistry panels are widely applied in the clinic or other healthcare settings (for example, occupational health) for several purposes and have been shown to also predict age-related outcomes but typically exhibit lower predictiveness than omic approaches[4]. There is thus a critical need for accessible and affordable BOA.

Recommendations

BOA applied at the individual level have a huge potential in preventative care, importantly as potential surrogate endpoint biomarkers or predictors that give patients an indication of how likely they will be able to 'feel, function, and survive' in the future (Food and Drug Administration (FDA) Biomarkers, EndpointS, and other Tools (BEST) Glossary[18]). The results from such biomarkers might persuade patients to adopt healthier lifestyles or consider geroprotective treatments. Assuming that their combination with existing individual indicators outperforms the use of the existing indicators alone, BOA have the advantage of focusing on broad health status rather than specific organs or diseases. This feature may have a greater potential to encourage a healthy lifestyle than biomarkers measuring risks for specific diseases that may be perceived as more distant or unlikely than aging itself. BOA can thus be included in health coaching and, in certain contexts, act as indicators for individuals to undergo more invasive screenings. BOA should thus be validated for their utility at the individual level, in addition to typical cohort-level validation approaches. This would allow BOA to be positioned alongside other biomarkers such as blood pressure as clinically useful indicators for individual patients. Future research should also focus on specific steps toward connecting biomarker readouts with specific actions or interventions that a person would benefit from, as interventions for increased epigenetic age or healthspan biomarkers are currently not well defined beyond general lifestyle recommendations. Although this in itself may be helpful, BOA without a clear responsiveness to interventions may have lower utility than those that warrant a clear action (Fig. 3a).

Finally, individual biomarkers for human health should be developed with accessibility and cost effectiveness in mind. This is particularly important when considering monitoring and optimizing health, for which few reimbursement options are currently in place, which hampers their broad accessibility.

Discussion

Working with a group of preclinical researchers and clinicians, we identified several key challenges for the successful translation of BOA. Based on these expert opinions, which begin to bridge the gap that currently exists between the developers and end users of BOA, we have formulated recommendations for potential next steps to overcome the current challenges, summarized in Table 2. Our results specifically emphasize that successful BOA should provide actionable insights, be affordable and available to broad populations and, importantly, be validated for both individual predictiveness and response to interventions. It is important to note that some very good predictors may still be poor surrogate measures, in particular when predictive and response properties have different mechanisms. For instance, increases in lean body and appendicular mass (assumed surrogate endpoints for functional measures) were not associated with improvements in leg press strength, gait speed or other health endpoints in a randomized controlled trial for a sarcopenia treatment; these and other examples of failed surrogate endpoints[43] underscore the need to ultimately understand causal mechanisms. It is also worth noting that biomarkers may exhibit different validity across different populations of participants, depending on underlying genetic, environmental or disease backgrounds. As such, translation of biomarkers will need to carefully consider the validity and utility of a given biomarker for specific settings, thoroughly validating biomarkers in diverse populations[4].

Our work identifies several opportunities for the application of BOA in translational geroscience but highlights the importance of generating sufficient evidence to demonstrate individual benefit. Such evidence will be critical for regulatory approval (for example, by the FDA and the European Medicines Agency) and is also reviewed by agencies such as the US Preventive Services Task Force or the UK National Institute for Health and Care Excellence that provide evidence-based recommendations and guidelines for patient care or individual prevention. Successful translation of BOA for clinical research or routine clinical practice, to optimize health and realize the potential of precision, personalized and/or preventive medicine may be accelerated by thorough cross-population validation and close cooperation between biomarker developers and/or researchers, clinicians and other key stakeholders. We note that challenges for translation of biomarkers may differ between established biomarkers that may already be routinely quantified and more recent omic or digital biomarkers, particularly in terms of cost, data and method availability and other factors. Translation of BOA may be facilitated by funding structures that enable subsidized biomarker measurements in large numbers of clinical (or routine) samples. Such sample collections could be used both to validate biomarkers and to develop new (response) BOA based on individuals who successfully responded to interventions. We provide several recommendations to incentivize data sharing and cooperation between researchers and clinicians. An additional opportunity for interdisciplinary cooperation is through engagement with the United Nations Decade of Healthy Ageing, which aims to bring together governments, civil society, international agencies, professionals, academia, the media and the private sector 'for ten years of concerted, catalytic and collaborative action' (https://www.who.int/initiatives/decade-of-healthy-ageing).

Although this work has identified actionable insights deserving immediate attention from the aging biomarker field, we acknowledge a key limitation: our respondent pool was selected based on their participation in the 2023 Biomarkers of Aging Symposium and predominantly comprised preclinical academic scientists. Although these experts are working at the cutting edge of aging biology, they may be relatively less attuned to practical considerations surrounding translation of BOA than clinicians and those working in industry. To mitigate this source of potential bias in our answers, we strove to carefully consider the input from clinician respondents while formulating our recommendations. As mentioned above, in moving forward, we must continue to promote deeper collaboration and cross-fertilization between preclinical and clinical researchers to ensure successful translation of BOA. Our respondents were also primarily from the USA and Europe; so further work may focus on bringing a more global perspective to the challenges in ensuring that the benefits of BOA in the clinic are broadly available to many populations. In a similar vein, the success of the implementation of BOA will depend in part on the opinion of the general population, that is, the individuals who will be ultimately tested with such tools. Translation of BOA will thus require close interaction of researchers and clinicians with multiple populations to learn their needs, expectations and attitudes toward these tools to develop generally useful and accepted BOA.

Conclusion

BOA have substantial potential to deliver on the promise of translational geroscience and personalized, preventive medicine in the context of aging. Further work remains to demonstrate their benefit and ultimately enable their translation. Our recommendations detailed above

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Table 2 | Overview of challenges and recommendations

Challenge	Recommendation	Example
(1) Data sharing for biomarker development and validation		
Successful biomarker translation relies on robust validation, which requires effective data sharing. However, incentives for researchers to properly annotate and share data are often lacking.	Funders, institutions, journals: improve infrastructure and support; reward data sharing. Individual researchers: lead by example. Consortia: establish and promote standards for data sharing and useful formats for data sharing.	Incentivization (funders and institutions): • Financially support and offer grant opportunities for data curation and harmonization, and include generation of high-quality shared datasets as a meaningful performance indicator for (tenure) promotion. Improved infrastructure (funders and institutions): • Provide guidance to navigate complex legal issues surrounding sharing health data, in particular regarding the EU GDPR and similar laws. • Create and maintain federated hubs and knowledge bases, including for standardized protocols. Leading by example (individual researchers): • Normalize the practice of sharing across nonprofit and commercial spaces. Standards on formats (consortia): • Establish standards for effective data sharing or useful formats. Last resort — penalization (funders, institutions and journals): • In case of repeated unwillingness to share data, hold investigators accountable, with consequences similar to research misconduct (for example, denial of grant or promotion, expression of concern or others).
(2) Heterogeneity in opinions regarding the most important criteria for BOA		
Experts disagree on the relative importance of criteria to evaluate BOA for most use cases.	Researchers and consortia: continue building consensus around the most important criteria for different applications of BOA.	Perform Delphi-based studies and benchmark various BOA across different settings.
(3) Age range for applications of BOA		
No consensus exists on whether BOA may be applied throughout lifespan or only later in life.	Researchers and consortia: study the potential of BOA to predict disease outcomes across the lifespan to guide future applications. Researchers and clinicians need to collaborate to balance fundamental features of aging with clinical practicality.	Validate biomarkers in different age groups. BOA could also be developed for specific age ranges.
(4) Minimal criteria for clinical use and implementation		
There is no clear consensus on the minimal criteria for clinical implementation of a biomarker of aging.	Researchers and consortia: set up robust clinical and technical validation experiments for BOA to link them to clear outcomes across multiple populations.	Develop and promote consensus frameworks for clinical implementation in close collaboration with clinicians.
(5) Positioning of BOA in the current disease-specific healthcare setting		
It is unclear how BOA can be used in healthcare settings that are focused on curing specific diseases.	Researchers and consortia: gradually implement BOA in existing healthcare systems. First replace chronological age as a risk stratifying tool, and ultimately take steps to shift toward health-optimized, preventive and pro-longevity healthcare. Governments: allow reimbursement for aging biomarker testing. Funders: fund studies focused on collecting aging biomarker measurements.	Use cases may include: • BOA to indicate screening or therapies • Monitoring response to interventions • Personalized prevention strategies.
(6) Connecting biomarkers with actionable insights in healthcare and preventive settings		
Few actionable insights currently exist for BOA, and their cost and accessibility remain prohibitive for widespread implementation.	Researchers and consortia: BOA need to be linked to clear actionable insights (for example, interventions) to improve their translational utility. Cost should also be considered.	Set up validation experiments to assess BOA for individual prediction of future health outcomes and monitor their responses to interventions. Fund methodology studies aimed at reducing assay costs and work closely with assay providers.

and summarized in Table 2 provide key areas of focus and guidance for the next steps to advance BOA to the clinic.

Methods

The questionnaire comprised ten questions aimed at identifying opinions on the relative importance of various criteria for different types of biomarkers in the context of translational use, appropriate age ranges for biomarker applications, what barriers and challenges respondents see for the clinical translation of BOA and what they believe are important next steps to overcome these barriers. The full questionnaire is provided in Supplementary Note 1.

Participants included a group of preclinical or clinical, academic or for-profit scientists (Fig. 1a) selected based on their participation as panelists or speakers at the 2023 Biomarkers of Aging Symposium ($n = 29$) or involvement with the Biomarker Consortium Roadmap Group ($n = 5$).

Participants were given the option to complete the questionnaire online or in a structured conversation. The majority completed the questionnaire online ($n = 27$); two respondents participated in a structured conversation. The responses on this questionnaire provided the basis for this Perspective. Questionnaire responses were reviewed independently by the drafting team members, and subsequent

collaborative discussion identified six core challenges and associated recommendations.

All coauthors of the paper either completed the questionnaire ($n = 29$) or provided additional input to the final challenges and recommendations presented in the current work ($n = 34$ coauthors in total). The paper and its recommendations were reviewed by all contributors. All participants consented to the use of their questionnaire responses for research and publication.

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Competing interests

M.M., V.S., M.P.S. and V.N.G. have filed a patent on measuring cellular aging. C.M.S.H. and M.W. are also affiliated with the Institute for Biomedical Aging Research and the Universität Innsbruck, Austria and C.M.S.H. is an honorary research fellow at the Department of Women's Cancer, EGA Institute for Women's Health, University College London, UK. C.M.S.H. and M.W. are shareholders of Sola Diagnostics and named as inventors on a patent on an epigenetic clock indicative of breast cancer risk. J.N.J. is also affiliated with the Sticht Center for Healthy Aging and Alzheimer's Prevention, Wake Forest University School of Medicine, Winston-Salem, NC, USA and the XPRIZE Foundation, Culver City, CA, USA. J.N.J. serves on the advisory board for the American Federation for Aging Research's Finding Aging biomarkers by Searching existing Trials (FAST) Initiative and on the editorial board of *Journals of Gerontology Series A*, *Biological Sciences*, *eLife* and *Experimental Gerontology*. D.W.B. is also affiliated with the Child Brain Development Network, the Canadian Institute for Advanced Research and the SocioMed Research Nucleus, Universidad Mayor, Santiago, Chile. D.W.B. is an inventor of DunedinPACE, a Duke University and University of Otago invention licensed to TruDiagnostic, and is consulting CSO and SAB chair of BellSant. A.H.-C. has built epigenetic aging metrics that are licensed by Elysium Health through Yale University. B.H.C. is a full-time employee of FOXO Technologies, which seeks to commercialize epigenetic technologies in the life insurance industry, owns stock in Illumina, the manufacturer of the DNA methylation arrays used for epigenetic BOA and is listed as a co-inventor in filed patents on commercial applications of epigenetic prediction models. A.A.C. is a founder, the president and a majority shareholder at Oken Health. K.F. is the CEO of BioAge Labs. P.O.F. is an employee and a stakeholder in Gero. A.Z. is the founder and the CEO of Insilico Medicine, a clinical-stage generative AI and robotics biotechnology company specializing in aging research. N.B. is the scientific director of the American Federation for Aging Research, is on the board of the executive committee of the Longevity Biotech Association and is an advisor on the board of the Academy for Health and Lifespan Research. D.P.K. has received a grant from Solarea Bio and royalties from Wolters Kluwer. D.P.K. sits on the scientific advisory board of Solarea Bio and has participated in the data safety monitoring board for the AgNovos Healthcare osteoporosis treatment trial. E.V. is a scientific cofounder of Napa Therapeutics and BHB Therapeutics, serves on the scientific advisory board of Seneque and is named as a co-inventor on a patent relating to an epigenetic clock robust to cell composition changes. A.B.M. is the chief medical officer of NU. V.S. is a cofounder, SAB chair and the head of research of Turn Biotechnologies. M.P.S. is a cofounder and a scientific advisor for Personalis, SensOmics, Q Bio, January AI, Fodsel, Filtricine, Protos, RTHM, Iollo, Marble Therapeutics, Crosshair Therapeutics and Mirvie. He is a scientific advisor for Jupiter, Neuvivo, Swaza and Mitrix. S.H. is a founder of the nonprofit Epigenetic Clock Development Foundation, which licenses patents surrounding epigenetic clocks. The Regents of the University of California is the sole owner of a patent application directed at GrimAge and other epigenetic clocks, on which S.H. is a named inventor.

Additional information

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