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Review

Insights on geroscience pre-clinical and clinical trials to promote healthy aging from the Intrinsic Capacity, Frailty and Sarcopenia Research Task Force 2025

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A B S T R A C T

The Intrinsic Capacity, Frailty and Sarcopenia Research (ICFSR) Task Force convened in March 2025 to discuss geroscience-oriented pre-clinical and clinical trials aimed at promoting healthy aging. Key topics included the use of aging biomarkers in clinical trials, senotherapeutics, metabolism-targeting medications, and therapeutic strategies beyond pharmacological approaches. The discussions highlighted the growing interest in, and accumulating evidence for, geroscience interventions. Several future challenges were identified, including the need for a deeper understanding of the biology of aging and the validation of aging biomarkers against relevant clinical outcomes, such as frailty and intrinsic capacity. Furthermore, to accelerate innovation in the field, there is a need to enhance clinical trial methodologies and harmonization—for example, by defining a minimum common dataset of biological, physiological, and clinical factors for geroscience clinical studies—and to foster a paradigm shift, particularly among regulatory authorities.

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1. Introduction

The increase in life expectancy observed in the most recent decades is largely attributed to significant societal and scientific transformations, particularly in public health measures and, to a lesser extent, to improvements in the prevention and treatment of chronic diseases [1]. Such a rise in life expectancy is an extraordinary accomplishment of the human race, but has been accompanied by an expansion of the period at the end of life characterized by diseases and disability [2]. Notably, gains in life expectancy have not been matched by equivalent improvements in healthspan. Without targeted and sustained public health interventions, this trajectory is likely to result in a significant escalation in the burden of disease and disability across individuals, families, communities, and health care systems.

Latest epidemiological cohorts indicate that fostering such improvements is feasible. For instance, research from the English Longitudinal Study of Ageing (ELSA) and the China Health and Retirement Longitudinal Study (CHARLS) reveals that recent cohorts of older adults exhibit higher levels of intrinsic capacity, the composite of physical and mental capacities, compared to prior generations [3]. In addition, recent data from the Health and Retirement Survey suggest that those individuals who experience a longer healthspan also ultimately benefit in terms of survival [4]. Despite these encouraging projections, large-scale, effective preventive strategies have yet to be incorporated into public health policies or research.

The geroscience hypothesis speculates that interventions that slow down the biological processes of aging can result in enhanced healthspan, promotion of healthy longevity, and compression of disability in the population [5]. If found to be effective, the geroscience strategy would revolutionize medicine through the identification of people at increased risk of chronic diseases before they become symptomatic and clinically identifiable.

However, some obstacles should be overcome. Any intervention that claims to slow down the pace of aging should be based on measures of aging that have been extensively validated in large, diverse populations. In this line, the current literature shows a growing body of research on biomarkers of aging, encompassing mainly molecular, physiological or functional, and digital indicators that serve diverse functions, especially relevant for geroscience clinical trials. These include:

- Predictive biomarkers, which identify individuals more likely to benefit from or be harmed by a treatment or exposure, or to experience certain outcomes without intervention;
- Prognostic biomarkers, which are associated with the worsening of clinical trajectories and outcomes in persons already experiencing specific aging-related conditions;
- Response biomarkers, which reflect the biological reaction of an individual to an exposure or intervention;
- Surrogate biomarkers, which can be used in clinical trials as substitutes for direct clinical measures; and
- Discovery biomarkers, which can be linked to biological pathways and may provide practical utility for identifying novel therapeutic targets and longevity interventions [6].

This rapid expansion of research on biomarkers will soon become the norm in clinical trial applications in multiple medical specialties [7,8]. However, it is important that the outcomes of these trials do not rely only on biomarkers but also include the broader clinical characterization of aging phenotypes in the recruited participants, including measures of functional status, frailty, mobility, and cognitive outcomes. The inclusion of these measures will provide robustness and credibility to the results of these trials, offering a biological face validity to the findings.

It is also important to recognize that existing literature already offers various preventive interventions that could significantly influence these outcomes, such as physical activity and dietary patterns [9]. Beyond education and raising public awareness of the importance of these

lifestyle approaches, a crucial aspect lies in identifying the biological transducers responsible for their effects. Understanding the underlying mechanisms may reveal novel therapeutic targets to extend healthspan and improve quality of life.

Building on this, the Intrinsic Capacity, Frailty and Sarcopenia Research (ICFSR) Task Force met on March 12, 2025, in Toulouse, France, to discuss these issues as well as recent advances in pre-clinical and clinical studies in geroscience. Following on insights from prior meetings, the Task Force confirmed its continued commitment to fostering collaboration, disseminating emerging evidence, and aligning global initiatives to accelerate innovation in the field [10–14].

The present manuscript highlights evidence from recent and ongoing pre-clinical and clinical trials focused on fundamental aging processes, based on the main topics discussed at the 2025 Task Force meeting. While this article does not aim to provide a comprehensive state-of-the-art of the field, it seeks to contextualize the results presented at the meeting by drawing on current literature, thereby offering a clearer understanding of these findings. For this reason, in addition to the studies presented during the meeting and their scientific background, we also incorporated other relevant articles from the PubMed and Scopus databases into this manuscript's references, when appropriate, to better interpret the proposed findings. The primary issues faced in the design and execution of these research efforts are also discussed in the paper. Finally, future directions are proposed to enhance and accelerate the translation of basic research findings into effective, evidence-based therapies. Fig. 1 illustrates a potential framework for pre-clinical and clinical studies in geroscience, based on the meeting results and discussions.

2. Key topics

2.1. Biomarkers of aging in clinical trials

As already mentioned, biomarkers play a crucial role in geroscience clinical trials. Surrogate biomarkers are essential because the direct assessment of healthspan, lifespan, and long-term functional status is impractical/unfeasible due to the time and costs involved. To be meaningful, surrogate biomarkers must correlate with clinical outcomes, predict them reliably, and demonstrate responsiveness to interventions.

Various generations of epigenetic aging clocks have shown promise in this sense [15]. They have proven to be dynamically responsive to non-pharmacological and pharmacological interventions while also possessing predictive power from a geroscientific perspective. This evidence supports their use also as surrogate biomarkers in clinical trials [16]. Interestingly, biomarkers such as the epigenetic clocks were originally developed to track biological aging. Recent literature suggests that they can also capture the effects of specific clinical conditions or treatments, such as schizophrenia or the antipsychotic drug clozapine [17]. This responsiveness, occurring both at the organismal level and within specific tissues, could be crucial not only for identifying beneficial treatments but also for detecting those that may require careful use, adjustment, or even avoidance from a geroscientific perspective. For instance, in the future, especially for individuals identified at higher risk of accelerated biological aging, this approach could guide the selection of therapeutically equivalent treatments, for example, in oncology, based on their differential impact on biological aging trajectories [18]. To accomplish this, there is a need for a broader use of these biomarkers not only in geroscientific clinical trials but also in those targeting age-related diseases, together with other clinical parameters in this line.

Another pertinent example of a potentially relevant biomarker in clinical trials is the novel blood-based epigenetic clock for intrinsic capacity, developed from the INSPIRE-T cohort. This clock, based on a DNA methylation (DNAm) predictor, correlates with both first- and second-generation epigenetic clocks, predicts all-cause mortality, and is associated with several relevant biological and clinical outcomes [19].

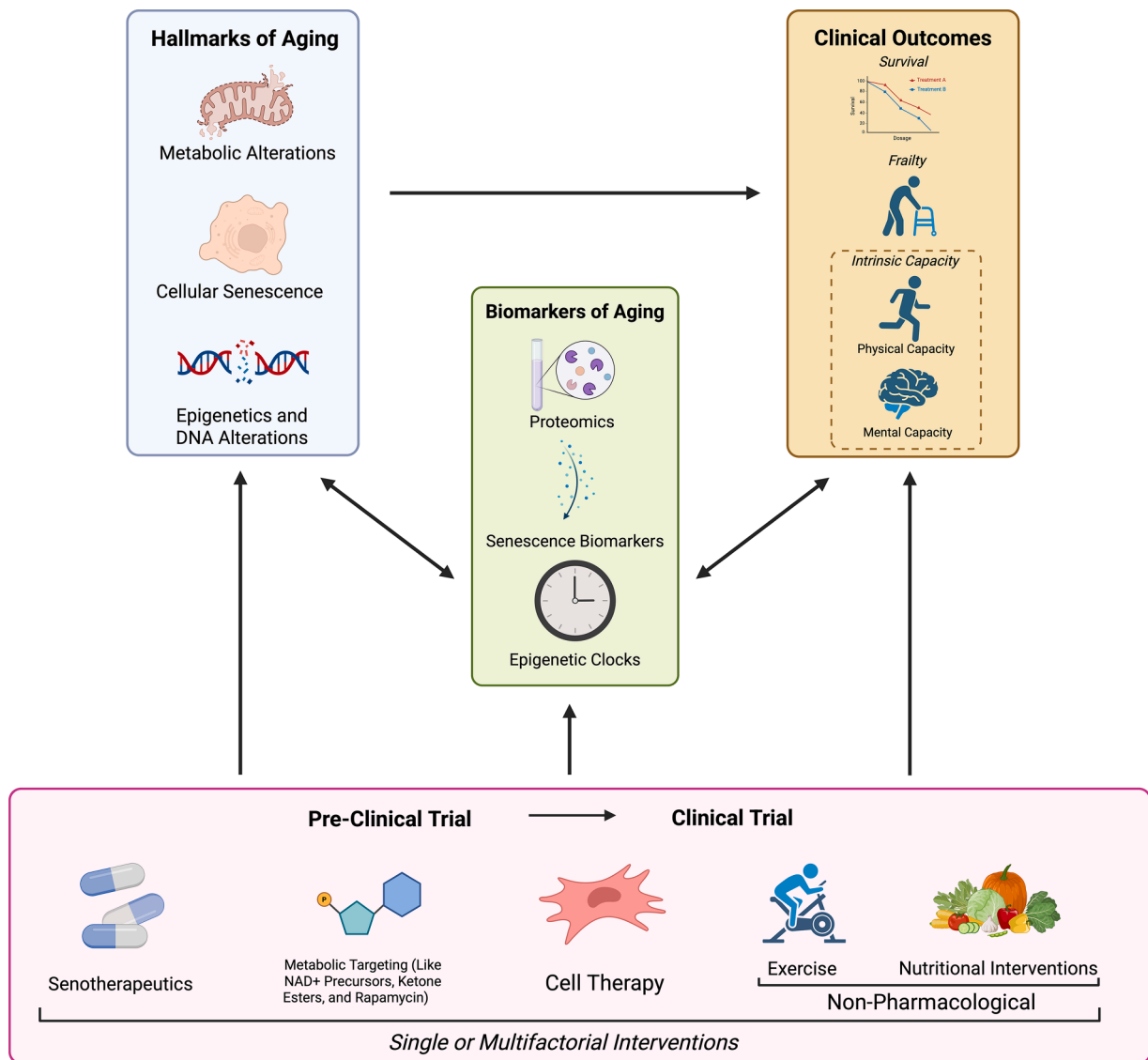


Fig. 1. Proposed paradigm for pre-clinical and clinical trials in geroscience.

The figure shows the key findings of the meeting report, with a focus on the hallmarks of aging, biomarkers, and clinical outcomes. It specifically shows the intimate connection between clinical outcomes, lifespan, healthspan, frailty, and intrinsic ability and the growing understanding of aging biology. In this context, some biomarkers are valuable tools, as they can serve a dual purpose: they may be discovery biomarkers, thereby improving our understanding of the biology of aging and identifying potential therapeutic targets, and, conversely, insights into the biology of aging can guide the identification of biomarkers useful across various clinical contexts and diseases. Moreover, biomarkers can thus be employed not only as diagnostic, predictive, and prognostic indicators but also as surrogate markers for meaningful outcomes, an aspect particularly relevant in the geroscience field. In this overall scenario, pre-clinical research offers mechanistic insights in this overall context by evaluating the ways in which interventions affect aging hallmarks and related biomarkers and starting to assess their possible effects on specific outcomes. Clinical trials then use validated biomarkers but also measurement of the aging phenotype and clinical evaluation to confirm these results in human populations. Therefore, single or multifactorial interventions could influence hallmarks and biomarkers of aging, together with clinical outcomes. Created in <https://BioRender.com>.

Other relevant biomarkers potentially useful in clinical trials focus on blood-based proteins [20]. For instance, a 12-year follow-up study involving 54,306 UK Biobank participants evaluated 1459 plasma proteins for their ability to predict all-cause mortality [20]. Fourteen proteins emerged as strong predictors and were linked to various age-related diseases [20]. Notably, participants in the highest quintile of mortality risk prediction experienced approximately 25 times more health events compared to those in the lowest quintile [20]. This platform could serve as another foundation for clinical trials aimed at improving health outcomes for patients.

There are several examples of practical applications of possible surrogate biomarkers in clinical trials [21–23]. A first example is the use of multi-omics biomarkers, ranging from epigenome to proteome,

metabolome, glycome, immune cytokines, iAge, and immune cell composition, to show the effect of therapeutic plasma exchange combined with intravenous immunoglobulin on biological age, especially in individuals with poorer initial health status [22].

Regarding multifactorial interventions, an excellent instance is the DO—HEALTH clinical trial, which assessed the effects of vitamin D, omega-3 supplementation, and exercise in older adults [23]. In this trial, omega-3 alone was found to slow several next-generation DNAm measures of biological aging, while the three treatments combined demonstrated additive benefits on PhenoAge, a second-generation epigenetic clock [24].

2.2. Cellular senescence and Senotherapeutics

Starting with basic research on the biology of aging, there is mounting evidence in the literature that cellular senescence, a relevant hallmark of aging, is not universally detrimental, playing also an essential role in processes such as tumor suppression [25]. In this line, senescent cells exhibit molecular heterogeneity that is context-, tissue-, and single-cell-dependent, which can influence their overall effects on organismal fitness [26], and can adopt either a beneficial helper phenotype, which supports tissue homeostasis and repair, or a harmful phenotype that contributes to tissue damage and age-related diseases [27]. For instance, regarding the first phenotype, polyploid bladder urothelial cells represent a long-lasting, helper form of senescence, as they adapt to chronic stress and maintain barrier integrity, resisting also several senolytic drugs, medications designed to selectively target and eliminate senescent cells [28]. Conversely, there are several examples of the detrimental role of senescence in various tissues and diseases, including osteoarthritis, Alzheimer's disease, and sepsis, showcasing the potential benefits of senotherapeutics in these contexts [29–32].

An overarching hypothesis that emerges from these data suggests that as we age, beneficial senescence tends to diminish while maladaptive senescence becomes more prevalent, ultimately undermining health [28].

Concerning interventions, senolytics, aimed at eliminating senescent cells, and senomorphics, focusing on modulating the production of senescent-associated secretory phenotype molecules, therefore reducing their deleterious effects on the organism, are starting to appear in the literature to treat a wide range of age-related diseases in clinical trials [33]. To guarantee that senotherapeutics have a major clinical impact, a critical assessment of the existing landscape of their clinical trials is paramount. To gain insight into the potential use of senotherapeutics in geroscience clinical trials, it is important to critically evaluate both design and processes. A prominent example is a phase 2 randomized controlled trial that examined the effects of intermittent senolytic therapy, based on dasatinib and quercetin, on bone metabolism in postmenopausal women [34]. Although no overall reduction in bone resorption was observed across the entire patient cohort, a potential therapeutic response was noted among a subsample of individuals with a high burden of senescent cells [34]. Additionally, subsequent analyses from this study pointed out the critical importance of identifying the most informative senescence-associated predictive biomarkers for patient selection in clinical trials, with, in this case, T-cell p16_{variant 5} and various components of the senescence-associated secretory phenotype being the most informative biomarkers to anticipate clinical response [35].

These findings strongly suggest that the success of these trials will depend heavily on our ability to target a study population of patients with diseases linked to cellular senescence, as indicated by proper biomarkers associated with senescence burden, since they are most likely to benefit from senotherapeutics, with a personalized approach to geroscience clinical trials [36]. Moreover, it is crucial to consider patient-specific characteristics, such as gender, in responses to senotherapeutic treatments, as highlighted by emerging pre-clinical data [31,37].

2.3. Metabolic targeting for healthy aging

Another significant theme in geroscience pre-clinical and clinical trials is the targeting of metabolic pathways that appear to be altered with aging. Among the most promising developments in this domain are studies investigating nicotinamide adenine dinucleotide (NAD⁺). Age-related declines in NAD⁺ levels have been implicated in a range of dysfunctions and chronic diseases [38]. NAD⁺ is essential for multiple resilience mechanisms that counteract damage accumulation with aging, including DNA repair, mitochondrial function, bioenergetic sensing, and other critical components of energetic metabolism [38].

Strategies to restore NAD⁺ levels include precursor supplementation, such as nicotinamide mononucleotide (NMN), or the inhibition of degradation [38]. Pre-clinical studies have shown that both approaches can enhance insulin sensitivity, muscle endurance, and myocardial resilience, collectively contributing to extended healthspan [38]. Early clinical trials involving NAD⁺ precursors, including the ones with NMN formulations, demonstrated a dose-dependent increase in blood NAD⁺ and its metabolites. However, in both strategies, the resulting precursor levels in plasma and tissue were variable, suggesting the involvement of alternative metabolic pathways in their effects [39,40]. One study linked NMN with reductions in total LDL cholesterol, body weight, and diastolic blood pressure among obese middle-aged and older adults [40]. Overall, NAD⁺ precursors appear to be safe, with some positive results in specific clinical contexts, such as in peripheral artery disease [38,41]. Nevertheless, their effectiveness may diminish during periods of high NAD⁺ turnover, such as during severe COVID-19 infections [42]. Therefore, further large-scale and long-duration clinical studies are essential to refine dosing strategies and confirm their efficacy, together with a better understanding of their mechanism of action.

Ketone esters, molecules naturally produced when breaking down fatty acids for energy, especially during low carbohydrate intake, fasting, or prolonged exercise, have recently raised great interest because they may serve as alternative energy sources by being oxidized in various tissues, including the brain [43]. This role is well established and particularly relevant in geroscience, as impaired bioenergetics is central in many age-related diseases [43,44]. Emerging evidence underscores that ketone esters are nutrient sensors and key participants in cellular signaling, both of which are critically involved in the aging process [43,44]. Building on this background, pre-clinical studies have demonstrated that a ketogenic diet in mice can reduce midlife mortality and enhance memory in older age, thereby extending overall longevity and healthspan [45,46]. β -hydroxybutyrate, a well-known ketone ester, has been shown to regulate protein solubility and selectively target misfolded proteins, including amyloid- β , which is implicated in neurodegenerative disease pathology [43,44]. Translating these findings into clinical practice, the Buck Institute's Ketone Ester (BIKE) proof-of-concept trial has confirmed the safety and tolerability of ketone esters in healthy older adults [47]. Further validation of these findings is currently underway in the BIKE study, along with larger clinical trials, such as Targeting Aging with a Ketone Ester for Function in Frailty (TAKEOFF, NCT06645847).

Studies in model organisms have demonstrated that rapamycin, an inhibitor of the mechanistic target of rapamycin (mTOR), extends lifespan and improves cognitive function, cardiac health, and physical performance. However, its clinical application in humans is constrained by notable adverse effects, including hyperglycemia, infection, and cataract [48,49]. To mitigate these risks, one proposed strategy involves the use of acute doses of rapamycin, which mainly inhibit mTORC1, thereby conferring healthspan benefits, while avoiding chronic treatment that may also suppress mTORC2 and disrupt metabolic regulation [50]. Indeed, intermittent or alternative rapamycin dosing schedules that selectively target mTORC1 extend lifespan in animal models while minimizing side effects [49]. A clinical trial in humans showed that weekly dosing of a rapamycin analog improved influenza vaccine responses in older adults and was well tolerated [51]. Building on this background, the phase 2 clinical trial, Everolimus Aging Study (EVERLAST) aims to determine whether 24 weeks of low-dose daily or weekly everolimus, a rapamycin analog, can safely enhance markers of metabolic, cardiac, cognitive, and physical aging in insulin-resistant adults aged 55–80. This study will also incorporate multi-omics profiling, comparing results with a young reference cohort [49].

2.4. Innovative therapeutic strategies beyond pharmacological approaches in geroscience

With an emphasis on improving healthspan and treating age-related

disorders, pre-clinical and clinical studies in geroscience are progressively investigating a variety of strategies outside of pharmacological approaches. The application of cell-based treatments, especially mesenchymal stem cells, is one such example. These stem cells are being explored for their immunomodulatory and regenerative properties, especially in osteoarthritis [52]. Pre-clinical studies have shown encouraging results, and clinical trials have also reported positive outcomes. However, uncertainties remain regarding, for example, the optimal cell source and dosage, and large-sample, multicenter randomized clinical trials may be needed to address these issues [53,54]. Moreover, new strategies, such as engineered constructs (e.g., TissueGene-C) [55] and placenta-derived stromal cells [56], aim to enhance the efficacy of cell-based therapies. However, further studies are needed to establish their clinical relevance in age-related diseases and clinical issues.

Another significant area of research in this line involves non-pharmacological interventions, particularly physical exercise, which has been shown to affect various hallmarks of aging, especially mitochondrial dysfunction [57]. Addressing mitochondria is particularly promising because physical performance in older adults strongly correlates with mitochondrial oxidative phosphorylation [58,59]. Moreover, these biological processes potentially reflect differences in patients' fitness, and they appear to be strongly associated with lifestyle habits such as physical exercise itself [60,61]. In fact, both pre-clinical and clinical evidence support the notion that exercise can help mitigate aging processes linked to mitochondrial dysfunction and reduced muscle energy capacity but also modulates the gut-microbiota-metabolite axis, ultimately enhancing functional status and overall health [60,62–64].

Exercise improves not only physical performance and mitochondrial function but also several age-related conditions, including lower urinary tract symptoms (LUTS), which are strongly linked to frailty and functional decline in men [65]. The relationship between frailty and LUTS appears bidirectional, with physical inactivity and sarcopenia as potential mediators [66]. Moreover, frailty also raises the risk of benign prostatic hyperplasia (BPH) progression and treatment-related adverse events [67]. Based on this, the PROUD clinical trial (NCT06225479) is investigating the effects of a 12-week remote exercise intervention in sedentary older men with LUTS attributed to BPH.

Nutritional interventions also represent a compelling non-pharmacological strategy [68]. Dietary restriction, particularly calorie restriction and intermittent fasting, in pre-clinical studies has shown promise in extending lifespan and healthspan by targeting aging hallmarks such as cellular senescence and mitochondrial dysfunction [69]. For instance, dietary interventions may modulate levels of inorganic polyphosphate, a key regulator of mitochondrial function that appears to decline with age in the brain and has been implicated in neurodegenerative processes [70,71].

As highlighted in the introduction, despite the growing clinical evidence supporting these non-pharmacological approaches, further investigation into their underlying molecular mechanisms is necessary before these discoveries are widely translated to prevention and care. A deeper understanding of the mediators of their effects is essential not only to identify the patient populations in which such interventions may be most biologically effective but also for laying the groundwork for developing future targeted therapies inspired by their modes of action.

Because of the multifactorial nature of aging, there is a growing interest in integrating diverse strategies, particularly some of the mentioned non-pharmacological interventions, to enhance healthspan. One notable example is the DO—HEALTH clinical trial [23], which was referenced earlier.

Another example is the Integrated Care for Older People (ICOPE) Intense pilot trial. This trial aims to address all six domains of intrinsic capacity (i.e., vitality, psychological, cognitive, locomotor, vision, and hearing) to enhance physical function and mitigate the biological mechanisms of aging, also incorporating the previously mentioned

treatment with ketone esters. The primary outcomes will assess the effect size on muscle, cognitive, and immune function [72,73].

A further example is the PREDIMED-Plus trial, a randomized, controlled, parallel-group study involving adult and older adult participants. The intervention group received a Mediterranean diet, physical activity promotion, and behavioral support for weight loss. A relevant objective was to improve HDL cholesterol efflux capacity and address immunosenescence [74]. In the intervention group, a significant enhancement in HDL cholesterol efflux capacity was observed, particularly among obese participants categorized by body mass index (BMI). Additionally, there was a reduction in the senescent T cell profile, especially in non-obese individuals [74]. Furthermore, cluster analysis identified three distinct response groups: late responders, non-responders, and early responders. Various factors influenced these responses, including sex, age, HDL cholesterol levels, body composition, and the previously mentioned BMI [74]. This last study, which incorporated evaluations of the biological effects of multicomponent interventions, underscores the importance of such analyses, echoing the considerations previously discussed regarding non-pharmacological approaches.

3. Future directions

Geroscience is rapidly emerging as a pivotal interdisciplinary field, driven by its potential to address the growing burden of chronic diseases and disability associated with increased life expectancy. As highlighted throughout this manuscript, recent advances in pre-clinical and clinical research have laid a promising foundation for translating aging biology into actionable strategies for prevention and care. However, the path forward is marked by several interconnected challenges. First of all, there is a need to further deepen our understanding of the biological processes that underlie aging, particularly those contributing to the onset of frailty and the maintenance/enhancement of intrinsic capacity. Even well-characterized processes such as cellular senescence require further investigation through diverse and integrative perspectives to enable meaningful clinical translation [28].

Biomarkers are essential for validating mechanistic hypotheses derived from pre-clinical models in humans, assessing the efficacy of treatments in clinical trials, and selecting the most appropriate patients for personalized therapies in alignment with the principles of precision medicine in geroscience. Additionally, to maintain comparability and reproducibility in this field, it is imperative to increase standardization in their use across studies, together with improving validation of these biomarkers on clinically significant outcomes, such as older individuals' physical and cognitive function [75]. Moreover, the use of multi-omics data combined with artificial intelligence models will definitely be paramount to further implement this field [6].

There is a strong need to conceptualize and develop a minimum dataset of biological, physiological, and clinical factors, as well as biospecimens that are widely accepted by the scientific community, to make progress in the design and interpretation of geroscience clinical trials. By encouraging standardization across clinical trials, enhancing data integration, and guaranteeing that significant biological materials are retained for upcoming analysis, the establishment of such a system would expedite translational efforts. In this line, frailty and intrinsic capacity are perfect candidates for a common clinical evaluation method. In fact, their multidimensional nature offers the opportunity for capturing the heterogeneity of the individual's health status and supporting the definition of age-related trajectories, as already highlighted in a previous edition of the ICFSR Task Force [12]. Other potential candidates for inclusion in a minimum dataset may include epigenetic clocks as biomarkers of biological aging and blood pressure variability, gait speed, VO_2 max, isokinetic strength, and body composition as physiological factors, as already partially highlighted in the existing literature [76]. Moreover, the so-called “social hallmarks of aging” are becoming increasingly prominent in the geroscience literature, as they

may influence key clinical domains such as intrinsic capacity and frailty and, more broadly, other relevant outcomes in this field [77]. This underscores the need to incorporate these factors into standardized evaluations of geroscience clinical trials, including parameters such as low socioeconomic status, minority status, adverse life events, adverse psychological states, and adverse health-related behaviors [77].

Furthermore, to strengthen the paradigm of geroscience, aging biomarkers developed within this field should be incorporated into a broader spectrum of clinical trials targeting age-related diseases, always accompanied by a common biobanking infrastructure and with the mentioned clinical evaluations.

As previously noted, the areas of geroscience that have gathered the most evidence from pre-clinical and clinical studies are senotherapeutics and metabolism-targeting therapies. A critical revision of the design and conduct of these studies is essential to inform and guide future research. Specifically, it is pivotal to learn from the processes that underpin these clinical studies, not only from the achievement of the outcomes, as exemplified previously in the development of senotherapeutic strategies.

Moreover, considering the complex and multisystem nature of aging [12,78], multifactorial interventions hold significant potential. The literature provides several successful examples of this type of clinical trial in adults and older adults, targeting specific aspects of healthspan such as cognitive function, as in the case of the FINGER study and the US POINTER randomized clinical trial [79,80]. Building on these examples is pivotal to designing geroscience clinical trials with multifactorial interventions. Furthermore, to ensure their effectiveness, it is crucial to adopt a personalized approach to patient stratification and to pursue mechanistic validation informed by biomarkers, strategies that are equally vital for non-pharmacological interventions, as they can help in identifying novel therapeutic targets.

Lastly, we believe a paradigm shift by international drug regulatory authorities is a crucial element that might actually accelerate the advancement of geroscience clinical trials, in line with the discussions at the previous ICFSR Task Force [8]. In particular, this would consist of moving beyond the approach of only evaluating treatments for specific illnesses and acknowledging the benefits of interventions that target the biological processes of aging to prolong healthspan and enhance

patients' functional status, both of which are, in our view, critical priorities at both the population and individual levels.

Box 1 summarizes the key proposals derived from the previous discussion, offering seven main guiding points for advancing research in geroscience.

4. Conclusions

The significant advancements made in the translation of geroscience to clinical practice are highlighted in this meeting report. However, there is still a substantial amount of work to be done in the field in this regard. Creating geroscientific frameworks that take into account assessments of frailty and intrinsic capacity is crucial for directing the development and use of successful interventions, which will ultimately enhance older persons' overall health. Based on these fundamental ideas, the ICFSR Task Force is committed to working with the larger scientific community to further this agenda over the next several years. This dedication guarantees the growing adoption of geroscience insights and their significant influence on clinical practice.

Disclosures

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Ethics approval statement and patient consent statement

NA

Box 1

Key proposals emerged from ICFSR Task Force meetings.

1. Enhance understanding of the biology of aging

Research on the biology of aging, with a focus on the fundamental mechanisms of frailty and intrinsic capacity, must be emphasized. Expanding our knowledge of well-known aging processes, like cellular senescence, and reevaluating their consequences is also essential. In order to provide an effective connection between laboratory discoveries and practical applications, clinical research should also study biomarkers to validate results from pre-clinical studies.

2. Advancement in the development and validation of aging biomarkers

The implementation of predictive, response, and surrogate biomarkers linked to key outcomes for older adults, such as frailty and intrinsic capacity domains, should be prioritized. Moreover, the application of large-scale omics data could be fundamental for the identification of discovery biomarkers associated with new targets for the meaningful clinical outcomes described before.

3. Biobanking and open-access data in geroscience clinical trials

To improve reproducibility, comparability, and cooperation in geroscience clinical trials, it is paramount to set up centralized biobanking and open-access data repositories. This could not just improve methodological issues of geroscience clinical trials but could really accelerate the achievement of evidence-based treatments.

4. Minimum dataset in geroscience clinical trials

A minimum dataset of standardized measures is highly relevant to improving methodology and design issues of geroscience clinical trials. It should include biological markers (such as epigenetic clocks), physiological measures (such as blood pressure variability, gait speed, VO₂ max, isokinetic strength, and body composition), and clinical parameters associated with aging. In this regard, a particular emphasis should be placed on frailty and intrinsic capacity as a shared outcome, due to their multicomponent and multifactorial nature and significance in the individual's health trajectories. Moreover, growing attention in this regard should be paid to the so-called "social hallmarks of aging."

5. Accelerate innovation in geroscience clinical trials

It is crucial to publish negative findings to promote innovation in the area by learning from research processes rather than concentrating only on the achievement of outcomes. To speed up geroscience clinical trials and their implementation in clinical practice, international drug regulatory entities should also move on from the conventional single-disease model and start assessing therapies meant to prolong healthspan and enhance patients' functional status.

6. Include the geroscience method in more comprehensive clinical research

Clinical trials for age-related disorders should incorporate aging biomarkers and clinical outcomes like intrinsic capacity and frailty. This integration would facilitate, for example, the identification of both potentially harmful and beneficial therapies from a geroscientific perspective, also allowing for the strategic repositioning of treatments.

7. Implement customized and biomarker-guided multifactorial interventions

Customized and multifactorial interventions, encompassing both pharmaceutical and non-pharmacological treatments, should be further developed, utilizing biomarkers for patient stratification and confirmation of mechanism of action. This approach may guide future pre-clinical research and the development of novel treatments by leveraging biomarkers to identify specific biological pathways involved in multifactorial interventions' efficacy.

The key considerations outlined in this box are designed to address critical aspects of advancing geroscience pre-clinical and clinical trials, drawing on discussions from previous Intrinsic Capacity, Frailty and Sarcopenia Research Task Force meetings [10–14] and building upon insights from the most recent session.

Data statement

NA

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Declaration of generative AI use

We declare no use of generative AI and AI-assisted technologies in scientific writing, and in figures, images, and artwork.

CRediT authorship contribution statement

Luca Tagliafico: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. **Marco Canevelli:** Writing – review & editing, Writing – original draft, Validation, Investigation, Conceptualization. **Philippe De Souto Barreto:** Writing – review & editing, Validation, Methodology, Conceptualization. **Matteo Cesari:** Writing – review & editing, Validation, Methodology, Conceptualization. **Luigi Ferrucci:** Writing – review & editing, Validation, Methodology, Conceptualization. **Bruno Vellas:** Writing – review & editing, Validation, Methodology, Conceptualization. **Yves Rolland:** Writing – review & editing, Validation, Methodology, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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References

- [1] Gianfredi V, Nucci D, Pennisi F, Maggi S, Veronese N, Soysal P. Aging, longevity, and healthy aging: the public health approach. *Aging Clin. Exp. Res.* 2025 Apr 17; 37(1):125.
- [2] Olshansky SJ. From Lifespan to Healthspan. *JAMA* 2018 Oct 2;320(13):1323.
- [3] Beard JR, Hanewald K, Si Y, Amuthavalli Thiyagarajan J, Moreno-Agostino D. Cohort trends in intrinsic capacity in England and China. *Nat. Aging* 2024 Dec 19;5(1):87–98.
- [4] Fabbri E, Candia J, Tanaka T, Moore AZ, Muratori P, Brugiavini A, et al. Dynamics of multimorbidity, health expectancy, and survival in middle aged and older individuals. *J. Gerontol. a Biol. Sci. Med. Sci.* 2025 Aug 23;80(9):glaf164.
- [5] Ferrucci L, Wilson DM, Donega S, Montano M. Enabling translational geroscience by broadening the scope of geriatric care. *Aging Cell* 2024;23(1):e14034.
- [6] Moqri M, Herzog C, Poganik JR, Justice J, Belsky DW, Higgins-Chen A, et al. Biomarkers of aging for the identification and evaluation of longevity interventions. *Cell* 2023;186(18):3758–75.
- [7] López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. *Cell* 2023;186(2):243–78.
- [8] Rolland Y, Sierra F, Ferrucci L, Barzilai N, De Cabo R, Mannick J, et al. Challenges in developing Geroscience trials. *Nat. Commun.* 2023 Aug 19;14(1):5038.
- [9] Quach A, Levine ME, Tanaka T, Lu AT, Chen BH, Ferrucci L, et al. Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. *Aging (Albany, NY)* 2017 Feb 14;9(2):419–46.
- [10] Rodriguez-Mañas L, Araujo De Carvalho I, Bhasin S, Bischoff-Ferrari HA, Cesari M, Evans W, et al. ICFSR Task Force perspective on biomarkers for sarcopenia and frailty. *J. Frailty. Aging* 2020;9(1):4–8.
- [11] Brasseur NK, De Cabo R, Fielding R, Ferrucci L, Rodriguez-Manas L, Viña J, et al. Identifying biomarkers for biological age: geroscience and the ICFSR Task Force. *J. Frailty. Aging* 2021;10(3):196–201.
- [12] Cesari M, Azzolino D, LeBrasseur NK, Whitson H, Rooks D, Sourdet S, et al. Resilience: biological basis and clinical significance — A perspective report from the International Conference on Frailty and Sarcopenia Research (ICFSR) Task Force. *J. Frailty. Aging* 2022;11(4):342–7.
- [13] De Souto Barreto P, Rolland Y, Ferrucci L, Arai H, Bischoff-Ferrari H, Duque G, et al. Looking at frailty and intrinsic capacity through a geroscience lens: the ICFSR & Geroscience Task Force. *Nat. Aging* 2023 Nov 20;3(12):1474–9.
- [14] Beaudart C, Cella D, Fielding RA, Rolland Y, Vellas B, Canevelli M. Patient-reported outcomes in sarcopenia: an ICFSR task force report. *J. Frailty. Aging* 2025;14(1):100010.
- [15] Duan R, Fu Q, Sun Y, Li Q. Epigenetic clock: a promising biomarker and practical tool in aging. *Ageing Res. Rev.* 2022;81:101743.
- [16] Sehgal R, Borrus D, Kasamoto J, Armstrong J.F., Gonzalez J, Markov Y, et al. DNAm aging biomarkers are responsive: insights from 51 longevity interventional studies in humans [Internet]. 2024 [cited 2025 May 13]. Available from: <http://biorxiv.org/lookup/doi/10.1101/2024.10.22.619522>.
- [17] Harvanek Z.M., Sehgal R., Borrus D., Kasamoto J., Priyanka A., Corley M.J., et al. Multidimensional epigenetic clocks demonstrate accelerated aging across physiological systems in schizophrenia: a meta-analysis [Internet]. 2024 [cited 2025 May 14]. Available from: <http://medrxiv.org/lookup/doi/10.1101/2024.10.28.24316295>.
- [18] Nannini DR, Cortese R, VonTungeln C, Hildebrandt GC. Chemotherapy-induced acceleration of DNA methylation-based biological age in breast cancer. *Epigenetics.* 2024 Dec 31;19(1):2360160.
- [19] Fuentealba M, Rouch L, Guyonnet S, Lemaitre JM, De Souto, Barreto P, Vellas B, et al. A blood-based epigenetic clock for intrinsic capacity predicts mortality and is associated with clinical, immunological and lifestyle factors. *Nat. Aging* 2025 [Internet]; Jun 4 [cited 2025 Jun 15]; Available from, <https://www.nature.com/articles/s43587-025-00883-5>.
- [20] Sethi A., Raj A., Wright K., Melamud E. Plasma proteomic determinants of common causes of mortality [Internet]. 2023 [cited 2025 May 13]. Available from: <https://www.researchsquare.com/article/rs-2626017/v1>.
- [21] Kim D, Kiprof DD, Luellen C, Lieb M, Liu C, Watanabe E, et al. Old plasma dilution reduces human biological age: a clinical study. *Geroscience* 2022;44(6):2701–20.
- [22] Fuentealba M, Kiprof D, Schneider K, Mu W, Kumaar PA, Kasler H, et al. Multi-omics analysis reveals biomarkers that contribute to biological age rejuvenation in response to single-blinded randomized placebo-controlled therapeutic plasma exchange. *Aging Cell* 2025;24(8):e70103.
- [23] Bischoff-Ferrari HA, Vellas B, Rizzoli R, Kressig RW, Da Silva JAP, Blauth M, et al. Effect of vitamin D supplementation, omega-3 fatty acid supplementation, or a strength-training exercise program on clinical outcomes in older adults: the DO-HEALTH randomized clinical trial. *JAMA* 2020 Nov 10;324(18):1855.
- [24] Bischoff-Ferrari HA, Gängler S, Wiecekorek M, Belsky DW, Ryan J, Kressig RW, et al. Individual and additive effects of vitamin D, omega-3 and exercise on DNA methylation clocks of biological aging in older adults from the DO-HEALTH trial. *Nat. Aging* 2025 Feb 3;5(3):376–85.
- [25] De Magalhães JP. Cellular senescence in normal physiology. *Science* (1979) 2024 Jun 21;384(6702):1300–1.
- [26] Lavarti R, Alvarez-Diaz T, Marti K, Kar P, Raju RP. The context-dependent effect of cellular senescence: from embryogenesis and wound healing to aging. *Ageing Res. Rev.* 2025;109:102760.
- [27] Tripathi U, Misra A, Tchkonina T, Kirkland JL. Impact of senescent cell subtypes on tissue dysfunction and repair: importance and research questions. *Mech. Ageing Dev.* 2021;198:111548.
- [28] Al-Naggar IM, Antony M, Baker D, Wang L, Godoy LDC, Kuo C, et al. Polyploid superficial uroepithelial bladder barrier cells express features of cellular

- senescence across the lifespan and are insensitive to senolytics. *Aging Cell* 2025;24(2):e14399.
- [29] Fusi G, Constantinides M, Fissoun C, Pichard L, Pers YM, Ferreira-Lopez R, et al. Senescence-driven inflammatory and trophic microenvironment imprints mesenchymal stromal/stem cells in osteoarthritic patients. *Biomedicines*. 2023 Jul 14;11(7):1994.
- [30] Fissoun C, Maroun G, Silva R, Milano M, Guibert B, Dagneaux L, et al. The ganglioside GD3 and its synthase (ST8SIA1) as novel senescence markers associated with osteoarthritis [Internet]. 2025 [cited 2025 May 14]. Available from: <http://biorxiv.org/lookup/doi/10.1101/2025.03.22.640206>.
- [31] Fang Y, Peck MR, Quinn K, Chapman JE, Medina D, McFadden SA, et al. Senolytic intervention improves cognition, metabolism, and adiposity in female APPNL-F/NL-F mice. *Geroscience* 2024 Aug 9;47(1):1123–38.
- [32] Lavarti R, Cai L, Alvarez-Diaz T, Medina-Rodríguez T, Bombin S, Raju RP. Senescence landscape in the liver following sepsis and senolytics as potential therapeutics. *Aging Cell* 2025;24(1):e14354.
- [33] Lelarge V, Capelle R, Oger F, Mathieu T, Le Calvé B. Senolytics: from pharmacological inhibitors to immunotherapies, a promising future for patients' treatment. *NPJ. Aging* 2024 Feb 6;10(1):12.
- [34] Farr JN, Atkinson EJ, Achenbach SJ, Volkman TL, Tweed AJ, Vos SJ, et al. Effects of intermittent senolytic therapy on bone metabolism in postmenopausal women: a phase 2 randomized controlled trial. *Nat. Med.* 2024;30(9):2605–12.
- [35] Farr JN, Monroe DG, Atkinson EJ, Froemming MN, Ruan M, LeBrasseur NK, et al. Characterization of Human senescent cell biomarkers for clinical trials. *Aging Cell* 2025;24(5):e14489.
- [36] Khosla S, Monroe DG, Farr JN. Towards a personalized approach in senolytic trials. *Nat. Aging* 2025 Sep 9.
- [37] Foster TC, Kumar A. Sex, senescence, senolytics, and cognition. *Front. Aging Neurosci.* 2025 Mar 4;17:1555872.
- [38] Bhasin S, Seals D, Migaud M, Musi N, Baur JA. Nicotinamide adenine dinucleotide in aging biology: potential applications and many unknowns. *Endocr. Rev.* 2023 Nov 9;44(6):1047–73.
- [39] Pencina KM, Lavu S, Dos Santos M, Beleva YM, Cheng M, Livingston D, et al. MIB-626, an oral formulation of a microcrystalline unique polymorph of β -nicotinamide mononucleotide, increases circulating nicotinamide adenine dinucleotide and its metabolome in middle-aged and older adults. *Le Couteur D, editor. J. Gerontol.* 2023 Jan 26;78(1):90–6.
- [40] Pencina KM, Valderrabano R, Wipperfurth B, Orkaby AR, Reid KF, Storer T, et al. Nicotinamide adenine dinucleotide augmentation in overweight or obese middle-aged and older adults: a physiologic study. *J. Clin. Endocrinol. Metabol.* 2023 Jul 14;108(8):1968–80.
- [41] McDermott MM, Martens CR, Domanchuk KJ, Zhang D, Peek CB, Criqui MH, et al. Nicotinamide riboside for peripheral artery disease: the NICE randomized clinical trial. *Nat. Commun.* 2024 Jun 13;15(1):5046.
- [42] Valderrabano RJ, Wipperfurth B, Pencina KM, Migaud M, Shang YV, Latham NK, et al. Dysregulated nicotinamide adenine dinucleotide metabolome in patients hospitalized with COVID-19. *Aging Cell* 2024;23(12):e14326.
- [43] Newman JC, Verdin E. β -Hydroxybutyrate: A signaling metabolite. *Annu. Rev. Nutr.* 2017 Aug 21;37(1):51–76.
- [44] Madhavan SS, Roa Diaz S, Peralta S, Nomura M, King CD, Ceyhan KE, et al. β -hydroxybutyrate is a metabolic regulator of proteostasis in the aged and Alzheimer disease brain. *Cell Chem. Biol.* 2025;32(1):174–91. e8.
- [45] Newman JC, Covarrubias AJ, Zhao M, Yu X, Gut P, Ng CP, et al. Ketogenic diet reduces midlife mortality and improves memory in aging mice. *Cell Metab.* 2017; 26(3):547–57. e8.
- [46] Roberts MN, Wallace MA, Tomilov AA, Zhou Z, Marcotte GR, Tran D, et al. A ketogenic diet extends longevity and healthspan in adult mice. *Cell Metab.* 2017; 26(3):539–46. e5.
- [47] Stubbs BJ, Stephens EB, Senadheera C, Peralta S, Roa-Diaz S, Alexander L, et al. Daily consumption of ketone ester, bis-octanoyl (R)-1,3-butanediol, is safe and tolerable in healthy older adults in a randomized, parallel arm, double-blind, placebo-controlled, pilot study. *J. Nutr., Health Aging* 2024;28(9):100329.
- [48] Miller RA, Harrison DE, Astle CM, Fernandez E, Flurkey K, Han M, et al. Rapamycin-mediated lifespan increase in mice is dose and sex dependent and metabolically distinct from dietary restriction. *Aging Cell* 2014;13(3):468–77.
- [49] Konopka AR, Lamming DW, PAC Investigators RAP, Grasso BA, Marrah RC, Decker S, et al. Blazing a trail for the clinical use of rapamycin as a geroprotector. *Geroscience* 2023 Oct 6;45(5):2769–83.
- [50] Arriola Apelo SI, Lamming DW. Rapamycin: an Inhibitor of aging emerges from the soil of Easter Island. *GERONA* 2016;71(7):841–9.
- [51] MANNICK JB, Del Giudice G, Lattanzi M, Valiante NM, Praestgaard J, Huang B, et al. mTOR inhibition improves immune function in the elderly. *Sci. Transl. Med.* 2014; 6(268) [Internet]Dec 24 [cited 2025 May 16] Available from, <https://www.science.org/doi/10.1126/scitranslmed.3009892>.
- [52] Shang Z, Wanyan P, Zhang B, Wang M, Wang X. A systematic review, umbrella review, and quality assessment on clinical translation of stem cell therapy for knee osteoarthritis: are we there yet? *Stem Cell Res. Ther.* 2023;14(1) [Internet]Apr 15 [cited 2025 May 17] Available from, <https://stemcellres.biomedcentral.com/articles/10.1186/s13287-023-03332-5>.
- [53] Copp G, Robb KP, Viswanathan S. Culture-expanded mesenchymal stromal cell therapy: does it work in knee osteoarthritis? A pathway to clinical success. *Cell Mol. Immunol.* 2023 Apr 25;20(6):626–50.
- [54] Cao M, Ou Z, Sheng R, Wang Q, Chen X, Zhang C, et al. Efficacy and safety of mesenchymal stem cells in knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Stem Cell Res. Ther.* 2025 Mar 7;16(1): 122.
- [55] Park EH, Seo J, Lee Y, Park K, Kim KR, Kim S, et al. TissueGene-C induces long-term analgesic effects through regulation of pain mediators and neuronal sensitization in a rat monoiodoacetate-induced model of osteoarthritis pain. *OsteoArthritis Cartilage* 2023;31(12):1567–80.
- [56] Maleitzke T, Zhou S, Hildebrandt A, Mobasher A, Fleckenstein FN, Halevy N, et al. A single placenta-derived mesenchymal-like stromal cell injection halts progression of primary knee osteoarthritis – First preclinical results from the PROTO consortium. *OsteoArthritis Cartilage* 2024;32:S48.
- [57] Adelnia F, Ubaida-Mohien C, Moaddel R, Shardell M, Lyashkov A, Fishbein KW, et al. Proteomic signatures of in vivo muscle oxidative capacity in healthy adults. *Aging Cell* 2020;19(4):e13124.
- [58] Coen PM, Jubrias SA, Distefano G, Amati F, Mackey DC, Glynn NW, et al. Skeletal muscle mitochondrial energetics are associated with maximal aerobic capacity and walking speed in older adults. *J. Gerontol.* 2013;68(4):447–55.
- [59] Lai Y, Ramirez-Pardo I, Isern J, An J, Perdiguerro E, Serrano AL, et al. Multimodal cell atlas of the ageing human skeletal muscle. *Nature* 2024 May 2;629(8010): 154–64.
- [60] Millan-Domingo F, Garcia-Dominguez E, Gambini J, Olaso-Gonzalez G, Viña J, MC Gomez-Cabrera. Diet and exercise in frailty and sarcopenia. *Molecular aspects. Mol. Aspects. Med.* 2024;100:101322.
- [61] Mau T, Barnes HN, Blackwell TL, Kramer PA, Bauer SR, Marcinek DJ, et al. Lower muscle mitochondrial energetics is associated with greater phenotypic frailty in older women and men: the Study of Muscle, Mobility and Aging. *Geroscience* 2024; 46(2):2409–24.
- [62] Izquierdo M, De Souto Barreto P, Arai H, Bischoff-Ferrari HA, Cadore EL, Cesari M, et al. Global consensus on optimal exercise recommendations for enhancing healthy longevity in older adults (ICFSR). *J. Nutr., Health Ag.* 2025;29(1):100401.
- [63] Cefis M, Marcangeli V, Hammad R, Granet J, Leduc-Gaudet JP, Gaudreau P, et al. Impact of physical activity on physical function, mitochondrial energetics, ROS production, and Ca²⁺ handling across the adult lifespan in men. *Cell Reports Med.* 2025;6(2):101968.
- [64] Yu C, Liu X, Li Y, Li S, Huang Y, Liu S, et al. Exercise remodels Akkermansia-associated eicosanoid metabolism to alleviate intestinal senescence: multi-omics insights. *Microorganisms.* 2025 Jun 13;13(6):1379.
- [65] Bauer SR, Cawthon PM, Ensrud KE, Suskind AM, Newman JC, Fink HA, et al. Lower urinary tract symptoms and incident functional limitations among older community-dwelling men. *J. Am. Geriatr. Soc.* 2022;70(4):1082–94.
- [66] Bauer SR, Scherzer R, Suskind AM, Cawthon P, Ensrud KE, Ricke WA, et al. CO-OCCURRENCE of lower urinary tract symptoms and frailty among COMMUNITY-DWELLING older men. *J. Am. Geriatr. Soc.* 2020;68(12):2805–13.
- [67] Bauer SR, Walter LC, Ensrud KE, Suskind AM, Newman JC, Ricke WA, et al. Assessment of frailty and association with progression of benign prostatic hyperplasia symptoms and serious adverse events among men using drug therapy. *JAMA Netw. Open.* 2021;4(11):e2134427. Nov 24.
- [68] Koppold DA, Breinlinger C, Hanslian E, Kessler C, Cramer H, Khokhar AR, et al. International consensus on fasting terminology. *Cell Metab.* 2024;36(8):1779–94. e4.
- [69] Grande De França NA, Rolland Y, Guyonnet S, De Souto Barreto P. The role of dietary strategies in the modulation of hallmarks of aging. *Ageing Res. Rev.* 2023; 87:101908.
- [70] Tagliafico L, Solesio ME. Could inorganic polyphosphate be a valid target against neuronal senescence? *Neural Regeneration Research* 2025 [Internet]Feb 24 [cited 2025 May 17]; Available from, <https://journals.lww.com/10.4103/NRR.NRR-D-24-01559>.
- [71] Tagliafico L, Da Costa RT, Boccia L, Kavehmoghaddam S, Ramirez B, Tokarska-Schlattner M, et al. Short-term starvation activates AMPK and restores mitochondrial inorganic polyphosphate, but fails to reverse associated neuronal senescence. *Aging Cell* 2024;23(11):e14289.
- [72] Berbon C, Rolland Y, Takeda C, Lafont C, Tavassoli N, De Kerimel J, et al. WHO ICOPE programme adherence of 8672 older age people over 2-years of follow-up. *J. Adv. Nurs.* 2025 Apr 7 jan.16740.
- [73] Berbon C, Takeda C, Balardy L, Lafont C, Tavassoli N, Carrie I, et al. Implementing the WHO ICOPE Program in Clinical Practice: three years of lessons from monitoring 27 082 participants using the ICOPE Monitor digital tool. *Lipsitz LA, editor. J. Gerontol., Series A* 2025 Feb 10;80(3):glae278.
- [74] Díez-Ricote L, Cuadrado-Soto E, Pastor-Fernández A, De La, Peña G, Martínez-Botas J, Castañer O, et al. Effect of a multifactorial weight loss intervention on HDL cholesterol efflux capacity and immunosenescence: a randomized controlled trial. *J. Am. Nutr. Assoc.* 2025 Feb 17;44(2):166–79.
- [75] Moqri M, Herzog C, Poganik JR, Ying K, Justice JN, Belsky DW, et al. Validation of biomarkers of aging. *Nat. Med.* 2024;30(2):360–72.
- [76] Perri G, French C, Agostinis-Sobrinho C, Anand A, Antarianto RD, Arai Y, et al. An expert consensus statement on biomarkers of aging for use in intervention studies. *Duque G, editor. J. Gerontol., Series A.* 2025 Apr 7;80(5):glae297.
- [77] Crimmins EM. Social hallmarks of aging: suggestions for geroscience research. *Ageing Res. Rev.* 2020;63:101136.
- [78] Cohen AA, Ferrucci L, Füllöp T, Gravel D, Hao N, Kriete A, et al. A complex systems approach to aging biology. *Nat. Aging* 2022 Jul 20;2(7):580–91.
- [79] Ngandu T, Lehtisalo J, Solomon A, Levälähti E, Ahtiluoto S, Antikainen R, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet* 2015 Jun 6;385(9984):2255–63.
- [80] Baker LD, Espeland MA, Whitmer RA, Snyder HM, Leng X, Lovato L, et al. Structured vs self-guided multidomain lifestyle interventions for global cognitive function: the US POINTER randomized clinical trial. *JAMA* 2025 Aug 26;334(8): 681.