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Review Article

Frailty in Modern Gerontology: Integrating Biological Age, Intrinsic Capacity, Resilience, and Functional Ability

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Abstract

Frailty is a central construct in clinical geriatrics that primarily captures vulnerability to stressors, while biological age, intrinsic capacity, physical resilience, and functional ability characterize complementary dimensions of aging. This conceptual narrative review synthesizes contemporary evidence, with particular attention to recent developments, and proposes a five-domain framework for clinical aging: biology, capacity, vulnerability, response, and function. Within this framework, biological age represents age-related biological change; intrinsic capacity, the physical and mental capacities available to the individual; frailty, vulnerability to stressors; physical resilience, the dynamic response to and recovery from stress; and functional ability, what a person can actually do within the environment. The domains are interrelated but not interchangeable and do not constitute a strictly linear causal pathway. The framework is not a diagnostic scale; rather, it is intended to improve interpretation of existing measures and generate testable hypotheses about multidimensional clinical aging.

Keywords: Frailty, Biological aging, Intrinsic capacity, Physical resilience, Functional ability

Introduction

Frailty has become a central construct in modern geriatrics and is used to characterize increased vulnerability to adverse outcomes when an individual is exposed to stressors[1,2]. The landmark approaches developed by Fried et al. and Rockwood and Mitnitski demonstrated that the same chronological age does not imply the same physiological reserve or risk of adverse outcomes[3,4]. Frailty assessment is now used not only in geriatrics but also in surgery, oncology, cardiology, and other areas of clinical medicine[1,2].

Frailty captures an important dimension of the aging phenotype—heightened vulnerability to stressors—but does not encompass all biological, functional, and adaptive dimensions relevant to aging. Biological age, intrinsic capacity, resilience, and functional ability have therefore gained increasing prominence as complementary constructs. These constructs partly overlap, but they should not be used interchangeably[5].

The second edition of the World Health Organization Integrated Care for Older People (ICOPE) guidance emphasizes assessment of cognitive, locomotor, vitality, sensory, and psychological capacities and the development of a personalized care plan[6-8]. Unlike frailty, intrinsic capacity describes the capacities available to an individual; these capacities may be supported by, but are not synonymous with, underlying physiological reserve. Contemporary evidence confirms that these constructs only partially overlap: low intrinsic capacity may occur without frailty, and frailty may coexist with relative preservation of individual intrinsic-capacity domains[9].

At the same time, clinical gerontology is converging with the biology of aging[10]. In 2025, Fuentealba et al. developed an epigenetic measure trained on clinical intrinsic capacity; the resulting measure was associated with functional and immunoinflammatory characteristics and predicted all-cause mortality[11]. In parallel, biological age is increasingly

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being reframed as a clinically interpretable risk construct rather than a literal difference between biological and chronological years[12]. Resilience adds a dynamic dimension by describing the ability to resist functional decline and recover after a health stressor[13].

The need to distinguish overlapping gerontological constructs has also been highlighted in JFSF. In 2026, an International Classification of Functioning, Disability and Health (ICF)-based framework was proposed to distinguish function, tissue pathology, and reserve across dysmobility syndrome, osteosarcopenia, and frailty[14]. Nevertheless, the relationship of frailty to biological age, intrinsic capacity, resilience, and functional ability remains conceptually fragmented.

The aim of this review is to define the boundaries among these constructs and to propose a five-domain framework for clinical aging in which frailty is positioned as the vulnerability domain within a broader multidimensional phenotype: biology, capacity, vulnerability, response, and function. The framework is intended to integrate existing measures rather than create another composite aging index.

The problem is not a shortage of measures but the absence of a common frame of reference for interpreting them. The same person may simultaneously have accelerated biological aging, decline in selected components of intrinsic capacity, frailty, a distinct recovery profile, and either preserved or impaired everyday function. Treating these constructs as synonyms risks misinterpreting both the mechanism of vulnerability and the clinical meaning of a given measurement. The central task of this review is therefore not to rank individual scales, but to clarify which dimension of aging each construct primarily captures.

Methods

This article was prepared as a conceptual narrative review. The review was developed with reference to the Scale for the Assessment of Narrative Review Articles (SANRA), including explicit justification of the review question, transparent description of the literature search, balanced presentation of evidence, and use of relevant sources[15].

A targeted, structured literature search was conducted in PubMed/MEDLINE, supplemented by manual searches of the reference lists of key publications, publisher websites, and international normative and guidance documents. Searches covered publications from January 1, 2000, through July 17, 2026; earlier studies were included when they were foundational to the constructs under consideration. Search terms were used in relevant combinations and included frailty, frailty syndrome, biological age, biological aging/ageing, aging clocks, intrinsic capacity, physical resilience, functional ability, healthy aging/ageing, geroscience, and older adults. Particular attention was given to studies directly comparing two or more of the constructs examined in this review.

Priority was given to international guidelines and consensus statements, systematic reviews and meta-analyses, large longitudinal and population-based studies, and conceptual publications that shaped contemporary definitions. Evidence published in 2024–2026 received particular attention because several constructs examined in this review, especially biological-aging measures, intrinsic capacity, and physical resilience, have undergone rapid conceptual and measurement development during this period. This emphasis was intended to capture recent developments and did not constitute a separate eligibility criterion; earlier foundational literature was retained to preserve definitional and historical context. Case reports, conference abstracts, studies unrelated to human aging, and publications without direct relevance to the review question were excluded.

Evidence was synthesized conceptually. No formal meta-analysis was undertaken because the purpose was to compare biological aging, intrinsic capacity, frailty, resilience, and functional ability and to define their clinical boundaries rather than estimate a pooled intervention effect. The five-domain structure was not imposed as a formal a priori classification for study selection. Rather, it was developed and refined iteratively during the conceptual synthesis, based on recurrent distinctions in the literature between biological state, available capacities, vulnerability to stressors, post-stressor response, and real-world functioning. These distinctions informed the final domains of biology, capacity, vulnerability, response, and function.

A hierarchy-of-evidence approach was used when selecting literature: where several sources addressed the same question, international consensus statements, systematic reviews, meta-analyses, and large longitudinal studies were prioritized. Conceptual and editorial articles were retained only when they introduced definitions or models directly relevant to the purpose of this review. Because the search was designed for conceptual synthesis rather than exhaustive quantitative comparison of interventions, the review was not conducted or registered as a systematic review.

Frailty: Measuring Vulnerability to Stressors

Frailty is defined as a clinical state of increased vulnerability in which reductions in strength, endurance, and physiological function increase the risk of dependency and death when an individual is exposed to a stressor[16,17]. The defining feature is therefore not age itself, but reduced ability to maintain homeostasis in the face of internal or external challenges.

Two approaches have been particularly influential. The Fried frailty phenotype comprises unintentional weight loss, exhaustion, weakness, slow walking speed, and low physical activity; three or more criteria indicate frailty and one or two indicate prefrailty[3]. The deficit-accumulation model conceptualizes vulnerability as the cumulative effect

of multiple health deficits and is operationalized through the Frailty Index[4]. The Clinical Frailty Scale provides a pragmatic global clinical assessment of health status and dependency[18]. These tools assess related phenomena but are not interchangeable[19].

The clinical relevance of frailty is well established: it is associated with mortality, hospitalization, falls, and functional decline[1-3,20-22]. Direct comparisons indicate that the Frailty Index and Fried phenotype have only moderate and broadly similar discrimination for all-cause mortality[23]. Frailty should also be distinguished from multimorbidity and disability: chronic diseases may contribute to frailty, and frailty may precede dependency, but these states overlap only partially.

Frailty is dynamic. In a meta-analysis of 16 cohort studies including 42,775 community-dwelling older adults, approximately 29% of participants transitioned to a more frail state, whereas 13.7% transitioned to a less frail state[24]. This supports partial reversibility of the clinical phenotype, but improvement in frailty status should not automatically be interpreted as reversal of fundamental biological aging.

A limitation of interpreting frailty in isolation is that two individuals with the same Frailty Index or Clinical Frailty Scale category may differ markedly in molecular aging, cognitive and sensory reserve, muscle function, social support, and capacity for recovery. Within the proposed framework, frailty therefore occupies the vulnerability domain: it answers the question how vulnerable is this person, but it does not replace assessment of biology, capacity, response, or function.

Distinguishing frailty from multimorbidity and disability is particularly important. These conditions can reinforce one another but are not equivalent: a person may have several chronic diseases and remain relatively resilient to stressors, whereas frailty may be present before substantial dependency in activities of daily living. Conversely, functional dependency may result from a focal neurological or sensory deficit without a global frailty phenotype. This distinction matters clinically because the same frailty category may arise through different pathways and require different clinical responses[5].

Heterogeneity of measurement tools remains an important problem. The physical phenotype emphasizes weakness, slowness, and low activity; the Frailty Index integrates a broad range of deficits; and the Clinical Frailty Scale relies on clinical judgment of overall health and dependency. The term frailty should therefore not be assumed to represent exactly the same measured phenotype across studies. Differences among instruments are especially relevant when comparing frailty prevalence and prognostic performance across clinical populations[17-19,25].

Biological Age: From Mechanisms of Aging to Clinical Meaning

Chronological age measures elapsed time but does not capture the individual pace of age-related change. The concept of biological age seeks to quantify this heterogeneity. At the level of measurement, biological-age metrics primarily characterize biological state or age-related dysregulation, whereas frailty instruments primarily operationalize clinical vulnerability to stressors. Conceptually, however, these domains are not biologically independent: multisystem dysregulation and loss of physiological reserve may contribute to the development of frailty[2,3,10,16,26].

The updated hallmarks of aging framework describes 12 interconnected mechanisms, including genomic instability, epigenetic alterations, loss of proteostasis and impaired autophagy, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem-cell exhaustion, chronic inflammation, and dysbiosis[10,27]. Because no single measure captures the multiple biological processes of aging, research has increasingly developed composite biomarkers and aging clocks to summarize age-related biological variation. These tools have primarily been developed for research and risk characterization, and their role in routine clinical practice remains uncertain[26,28,29].

By 2026, aging clocks encompass epigenetic, proteomic, metabolomic, clinical, imaging-based, and multimodal models[28,29]. Increasing attention is being directed toward organ-specific aging because different organs within the same individual may follow distinct aging trajectories[30,31]. There is, however, no single true biological age: different clocks are trained on different outcomes and capture different aspects of aging.

Methodological maturity remains limited. A 2026 systematic review of 59 studies describing 81 clinical aging-clock models found that 38.3% had undergone neither internal nor external validation, while most had a high risk of bias or limited applicability[32]. The contemporary question is therefore shifting from how many biological years older or younger a person appears to what clinically meaningful risk a given measure captures[12].

Associations between biological age and frailty are not consistent across all models. A meta-analysis of 24 studies including 28,325 participants found more consistent associations with frailty for several later-generation epigenetic clocks and measures of the pace of aging, whereas simple deviation of DNA methylation age from chronological age was not consistently associated with frailty[33]. These findings support distinguishing the measurement domains without implying biological independence: biological-age measures characterize aspects of underlying biological state, whereas frailty measures primarily characterize clinically expressed vulnerability. Biological dysregulation

may contribute to frailty, but the two constructs are not interchangeable and may show only partial concordance at the individual level[3,10,33].

At present, aging clocks should be regarded as promising complements rather than substitutes for clinical assessment. Their value will depend on whether they predict loss of capacity, development of frailty, impaired recovery, or functional decline beyond information already available from conventional clinical measures[26,29,32].

Historically, early epigenetic clocks were optimized primarily to reproduce chronological age[34,35]. Later generations were trained on mortality-related and phenotypic outcomes, whereas newer approaches increasingly quantify the pace of aging and organ-specific trajectories[30,31,36-38]. This is a fundamental shift: a biomarker becomes potentially useful when it captures future clinically meaningful risk or is responsive to change that matters for healthspan.

The study by Fuentealba et al. is conceptually important in this context because the epigenetic model was linked to intrinsic capacity rather than using chronological age as its sole endpoint[11]. This approach suggests a possible direction for biomarkers of aging: moving from an abstract age estimate toward molecular measures linked to capacity, frailty, resilience, or disability-free survival. Such models, however, cannot yet replace direct clinical assessment.

Intrinsic Capacity: Assessing Preserved Capacities

The World Health Organization defines intrinsic capacity (IC) as the composite of all physical and mental capacities available to an individual. The ICOPE approach assesses cognition, mobility, vitality, vision, hearing, and psychological capacity[6-8]. If frailty asks how vulnerable a person is, intrinsic capacity asks what capacities are currently available.

This perspective complements a disease-oriented model. Multimorbidity does not necessarily imply substantially reduced intrinsic capacity, whereas a person with relatively few diagnosed diseases may have important impairments in mobility, nutrition, cognition, or sensory function. Intrinsic-capacity assessment may therefore identify specific, potentially modifiable deficits before marked dependency develops[39].

The prognostic relevance of intrinsic capacity is supported by longitudinal evidence. Meta-analytic data indicate that higher intrinsic capacity is associated with a lower risk of subsequent impairment in basic and instrumental activities of daily living and with lower mortality[40,41]. Another meta-analysis found that lower overall intrinsic capacity and deficits in individual domains were associated with later functional disability, with the most consistent associations observed for locomotion, cognition, psychological capacity, and vitality[42].

Intrinsic capacity and frailty are closely related but are not opposite ends of a single continuum. In a study of 3,246 older participants, in which frailty was operationalized using a 32-item Frailty Index, groups with low intrinsic capacity but no frailty and frailty without low intrinsic capacity were both identified, with overlap increasing only in the oldest age groups[9]. This empirical finding is consistent with conceptual work treating frailty and intrinsic capacity as distinct but related constructs[43]. Joint assessment may therefore distinguish preserved capacities from global vulnerability.

Within the five-domain framework, intrinsic capacity corresponds to the capacity domain. Its relationship with biology and vulnerability is probabilistic and bidirectional: biological changes can reduce individual capacities, but clinical vulnerability is also shaped by disease, behavior, and the environment.

Intrinsic capacity should also be viewed as a dynamic trajectory. Individual domains may decline at different rates, and maintenance or improvement of overall intrinsic capacity is associated with more favorable functional outcomes[40,44]. This makes intrinsic capacity particularly relevant to preventive gerontology: rather than only classifying an individual as frail or non-frail, clinicians can identify which capacities are already declining and may be amenable to intervention.

An important distinction in emphasis is that intrinsic capacity is commonly framed in asset-oriented terms, focusing on both preserved and impaired capacities, whereas frailty instruments are typically framed around vulnerability, deficits, or phenotypic features associated with adverse outcomes. This contrast is partly conceptual and terminological rather than absolute: the same frailty measure can also be interpreted from the opposite direction as reflecting greater or lesser robustness. The two approaches are therefore complementary rather than inherently deficit- versus asset-based. Frailty supports vulnerability stratification, whereas intrinsic capacity helps identify specific capacities on which preventive or rehabilitative care can be built.

Physical Resilience: A Dynamic Response to Health Stressors

Physical resilience describes the ability to resist functional decline and recover after a health stressor such as infection, surgery, trauma, or hospitalization[13,45,46]. Its fundamental distinction from frailty is its dynamic nature: frailty characterizes baseline vulnerability, whereas resilience becomes observable through the trajectory that follows a specific stressor.

The Study of Physical Resilience and Aging (SPRING) conceptualizes resilience as the ability to withstand a stressor and return rapidly to the pre-stressor or a higher level of function, using repeated measurements before and after surgical, transplantation-related, and other clinical stressors[45,47]. The magnitude of the initial decline, speed of recovery, and completeness of recovery are

conceptually important.

Frailty and resilience are not simple inverses. Greater frailty may reduce the probability of favorable recovery, but baseline vulnerability does not fully determine the subsequent trajectory. Two patients with similar preoperative frailty may therefore experience substantially different recovery patterns[48,49].

Measurement of resilience is itself not yet standardized. In 2026, a direct comparison of recovery-trajectory and expected-recovery-differential approaches in 170 older adults undergoing total knee arthroplasty showed the greatest agreement for clearly high or low resilience, with less agreement for intermediate recovery patterns[50]. This underscores the need to consider both the type of stressor and the functional outcome being measured.

Clinical data from hospitalized older adults also support relationships among physiological reserve, intrinsic capacity, and physical resilience[51]. Within the proposed framework, resilience corresponds to the response domain: how does the person respond to and recover from a stressor? This domain adds a temporal dimension that is absent from most static assessments.

Physiological reserve is not treated as a separate sixth domain in the proposed framework. Rather, it is considered a cross-cutting underlying property that may contribute to several domains simultaneously: reserve may support intrinsic capacity, influence vulnerability to a stressor, and shape both resistance and recovery after that stressor. This distinction also avoids equating reserve with resilience itself. Physiological reserve refers to resources that may enable an adaptive response, whereas physical resilience is expressed dynamically through the observed trajectory following a specific stressor[45,46,51].

Resilience cannot be inferred reliably from a single baseline measure. A history of recovery after pneumonia, surgery, injury, or hospitalization may contain information that a conventional static frailty assessment does not capture. In the future, digital monitoring and repeated objective measures of mobility may allow recovery trajectories to become part of routine assessment, but such approaches require standardization and evidence of incremental prognostic value[52].

It is also useful to distinguish resistance from recovery. Some individuals show little initial decline after a stressor, whereas others show a substantial decline followed by rapid return to baseline. Both patterns may indicate relatively high resilience but reflect different physiological response strategies. This is another reason not to reduce resilience to the simple opposite of frailty[46,49,52].

Functional Ability: The Interaction Between the Individual and the Environment

Within the World Health Organization framework for healthy ageing, functional ability refers to the health-related attributes that enable people to be and to do what they value; it emerges through interaction between intrinsic capacity and the physical and social environment[7,53]. Accordingly, the same level of intrinsic capacity does not necessarily result in the same degree of real-world independence.

In the Longitudinal Aging Study Amsterdam, higher intrinsic capacity was associated with a lower likelihood of functional decline over six years, and characteristics of the physical environment modified this relationship[54]. Adapted housing, accessible transport, assistive technologies, and social support may partially compensate for limitations in internal capacity.

Functional ability is broader than the absence of disability or preservation of activities of daily living and instrumental activities of daily living. It encompasses mobility, participation, decision-making, and the pursuit of individually meaningful goals. Within the five-domain framework, it corresponds to the function domain: what the person is actually able to do in the circumstances of daily life.

The concept of functional ability therefore shifts the endpoint toward what a person can do in the context of their own life. Functional assessment should extend beyond activities of daily living and instrumental activities of daily living to include mobility, participation, decision-making, and achievement of individually meaningful goals. From this perspective, a clinically successful intervention may improve function through environmental modification or support even when biological age is unchanged[7,53,54].

Integrating the Constructs: A Five-Domain Framework for Clinical Aging

Modern gerontology offers numerous measures of aging, yet conceptual overlap among them complicates interpretation. Frailty and intrinsic capacity have already been proposed as complementary rather than competing approaches[43,55]. We extend this logic by proposing a five-domain framework: biology, capacity, vulnerability, response, and function (Figure 1; Table 1).

The biology domain captures molecular, cellular, tissue, organ, and systemic age-related changes and is represented by biological age and related biomarkers. Capacity describes the physical and mental capacities available to the individual and is represented by intrinsic capacity. Vulnerability corresponds to frailty and describes susceptibility to an adverse response when exposed to a stressor. Response is represented by resilience and describes resistance and recovery over time. Function corresponds to functional ability and reflects real-world functioning in interaction with the environment.

The five domains are not intended to represent constructs of identical ontological or measurement status. Biological age is primarily biomarker-based, frailty is a clinical vulnerability construct, resilience is inherently dynamic and stressor-dependent, and functional ability

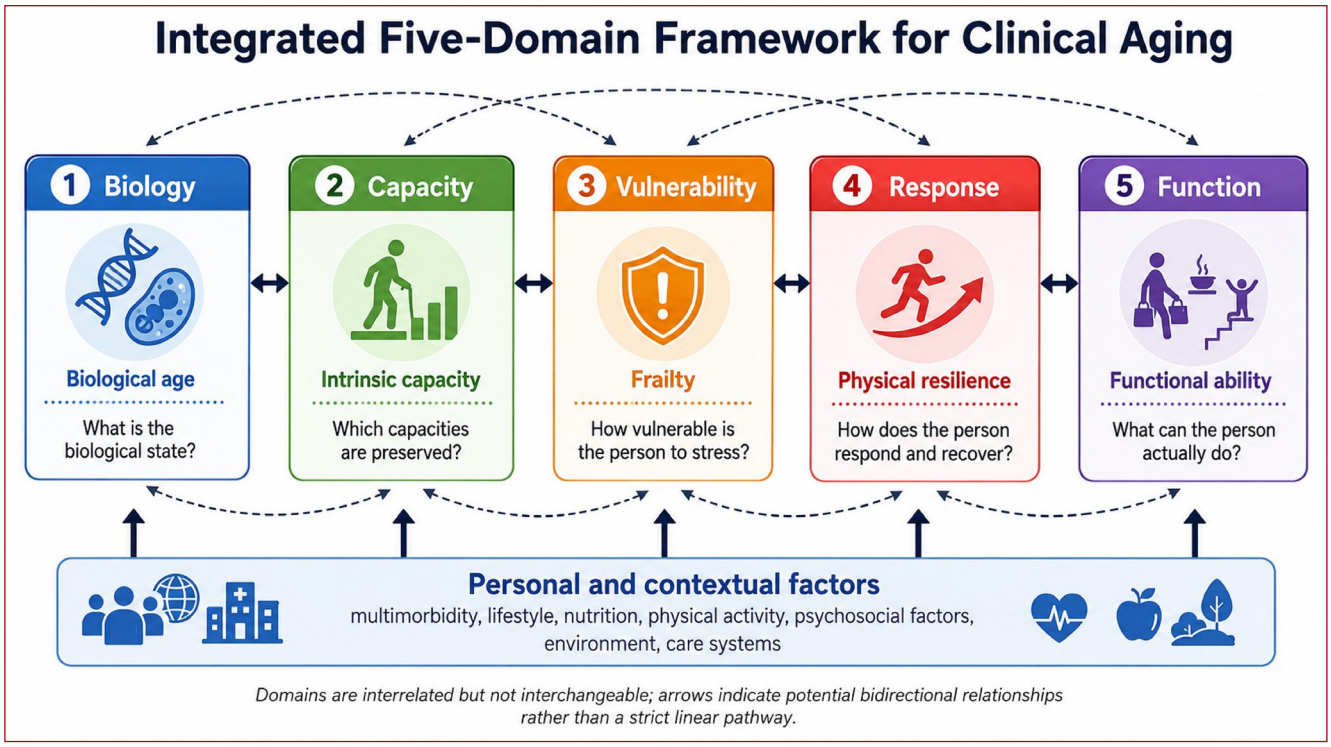

Figure 1. Integrated Five-Domain Framework for Clinical Aging. The framework distinguishes five complementary domains: biology (biological age), capacity (intrinsic capacity), vulnerability (frailty), response (physical resilience), and function (functional ability). The domains are interrelated but not interchangeable. Arrows indicate potential bidirectional relationships rather than a linear causal pathway. Personal and contextual factors may influence all five domains. Physiological reserve is conceptualized as a cross-cutting property that may influence capacity, vulnerability, and response rather than as a separate domain.

Domain	Construct	Central question	What it reflects	Assessment examples	Key limitation
Biology	Biological age	What is the biological state?	Molecular and organ-level aging	Aging clocks	Limited validation/ actionability
Capacity	Intrinsic capacity	Which capacities are preserved?	Physical and mental capacities	ICOPE domains	Variable operationalization
Vulnerability	Frailty	How vulnerable is the person to stress?	Homeostatic vulnerability	Fried phenotype; Frailty Index; CFS	Tools not interchangeable
Response	Physical resilience	How does recovery occur?	Post-stressor trajectory	Repeated recovery measures	Requires longitudinal data
Function	Functional ability	What can the person actually do?	Real-world functioning	ADL/IADL; participation	Environment-dependent

***Abbreviations**: ADL, activities of daily living; CFS, Clinical Frailty Scale; IADL, instrumental activities of daily living; ICOPE, Integrated Care for Older People.*

Table 1. Distinguishing the Five Domains of Clinical Aging.

Profile	Interpretation	Potential clinical relevance
Accelerated biological age + preserved intrinsic capacity + low frailty	Biological change precedes overt clinical vulnerability	Hypothesis of preclinical risk; prospective validation required
Low intrinsic capacity without frailty	Loss of capacity precedes global vulnerability	Potential window for earlier intervention
Frailty + preserved intrinsic-capacity domains	Vulnerability does not imply global loss of capacity	Specific drivers of frailty should be identified
Frailty + high resilience	Baseline vulnerability coexists with favorable recovery	Frailty alone may overestimate risk of persistent decline
Low frailty + poor resilience	Static assessment fails to capture limited recovery	Repeated post-stressor measurements may add information
Reduced intrinsic capacity + preserved function		

Table 2. Examples of Discordance Between Aging Domains and Their Potential Clinical Interpretation.

is relational and environment-dependent. Their inclusion within the same framework reflects complementary clinical questions rather than equivalence of measurement structure.

The boundaries among the five domains should therefore be understood as interpretive rather than mechanistic. Biological dysregulation may contribute to vulnerability, physiological reserve may influence both capacity and response, and environmental factors may modify functional ability without equivalent changes in the other domains. The framework distinguishes the primary clinical question addressed by each construct without implying that the underlying processes are biologically independent.

The sequence biology -> capacity -> vulnerability -> response -> function is conceptual rather than a linear causal chain. Bidirectional relationships exist among domains, and multimorbidity, nutrition, physical activity, treatment, psychosocial factors, and the environment may influence several domains simultaneously. For example, severe illness may alter biological markers, reduce intrinsic capacity, and increase frailty, whereas incomplete recovery from a stressor may subsequently worsen capacity and function.

Discordance among domains may provide particularly useful clinical information (Table 2). Accelerated biological age may coexist with preserved intrinsic capacity and low frailty; low intrinsic capacity may precede global vulnerability; a frail individual may recover better than expected after a stressor; and preserved intrinsic capacity may not guarantee high functional ability in an unfavorable environment. Such combinations should not automatically be interpreted as measurement error but as potentially informative variants of an individual aging phenotype.

We propose the term multidimensional clinical aging phenotype to describe an individual's configuration across the five domains. This is deliberately different from creating a single composite score: one number would inevitably obscure distinctions among biological state, preserved capacities, vulnerability, recovery potential, and function.

The proposed framework is not a new diagnostic scale and should not be used as a stand-alone basis for clinical decisions before prospective validation. Its purpose is to provide a common frame of reference for existing measures and to generate testable hypotheses about whether multidimensional assessment improves prediction of functional decline, hospitalization, and recovery beyond frailty assessment alone.

The five-domain framework does not imply that every patient requires costly molecular testing. In current practice, biology may remain predominantly a research domain, whereas capacity, vulnerability, and function are accessible to clinical assessment and response can be characterized longitudinally. The framework is therefore scalable and can serve as a conceptual architecture even when not every domain is quantified.

Discordant profiles should be a particular focus of future validation. If two individuals have the same degree of frailty but differ substantially in intrinsic capacity or resilience, their risks and responses to intervention may also differ. Likewise, accelerated biological age in a person with preserved function may carry a different implication than the same value in the presence of low intrinsic capacity and frailty. Testing these interactions will determine whether the multidimensional phenotype provides information beyond a single summary measure.

Clinical Implications: From Frailty Screening to Multidimensional Aging Assessment

The practical value of frailty lies in rapid identification of increased risk, but a positive frailty screen should be viewed as the beginning rather than the end of assessment. A 2026 systematic review reported frailty prevalence ranging from 4.4% to 90% across clinical settings depending on the instrument used, with substantial differences in prognostic performance among tools[56].

The five-domain framework does not replace Comprehensive Geriatric Assessment (CGA); rather, it can help interpret its findings. Once vulnerability has been identified, potential drivers should be explored, including impaired mobility and muscle function, cognitive and sensory deficits, nutritional problems, multimorbidity, polypharmacy, and psychosocial factors. A meta-analysis of 18 randomized trials in hospitalized older adults with frailty found that CGA was associated with a lower risk of decline in activities of daily living and lower mortality, although the authors emphasized limitations in the evidence base[57,58].

The capacity domain allows clinicians to move from a global frailty category toward specific preserved and impaired capacities. The biology domain currently has a predominantly research role: an aging clock should influence clinical decisions only after demonstrating incremental value beyond chronological age, disease burden, frailty, and functional status. The response domain is particularly relevant after surgery or hospitalization, when repeated measurements can characterize the actual recovery trajectory.

Functional ability represents a major clinically meaningful outcome of aging. Individuals with the same degree of frailty may require different interventions depending on whether independence is limited primarily by internal capacity loss, poor recovery, or an unfavorable environment. Frailty therefore remains central to risk stratification, but its optimal interpretation requires an understanding of the other domains.

In practice, the framework can be expressed as a sequence of clinical questions. First, vulnerability is assessed: is frailty present and how severe is it? Capacity is then considered: which physical and mental capacities are preserved and which are declining? In patients who have experienced a major stressor, response is characterized by the magnitude of decline and completeness of recovery. Function shows how these processes are expressed in everyday life. As biomarker panels and aging clocks become clinically validated, biology may add mechanistic information and earlier risk stratification.

This approach is consistent with, but does not duplicate, CGA. CGA is a clinical process of multidimensional assessment and care planning, whereas the five-domain framework is intended to organize and interpret different levels of information. It may help prevent an isolated frailty scale, molecular biomarker, or activities-of-daily-living score from being mistaken for a complete description of an individual's aging state[57,58].

Previous conceptual work has already linked frailty with intrinsic capacity, physical resilience, and geroscience, supporting the view that these constructs are complementary rather than interchangeable[59-62]. The present framework extends these approaches by explicitly distinguishing biological state, available capacity, vulnerability, post-stressor response, and real-world function as five separate but interacting dimensions within a single conceptual architecture for clinical aging.

Research Priorities and Future Directions

The first priority is to test prospectively whether simultaneous assessment of biology, capacity, vulnerability, response, and function provides incremental prognostic information beyond frailty alone. Relevant outcomes include functional decline, hospitalization, falls, recovery after stressors, institutionalization, and mortality. Discordant phenotypes are of particular interest because they may reveal clinically relevant information that is obscured by a single summary measure.

A second priority is measurement harmonization rather than adoption of a single universal instrument. Frailty is operationalized using the physical phenotype, Frailty Index, Clinical Frailty Scale, and numerous other instruments; intrinsic capacity and resilience likewise have heterogeneous operational definitions. Progress will require explicit definition of the construct being measured, prespecification of instruments and cut points, consistent reporting of core measurement characteristics and outcomes, and development of calibration or cross-walk approaches where multiple validated instruments coexist. For resilience, reporting should additionally specify the stressor, the timing and definition of the pre-stressor baseline, follow-up intervals, the outcome used to characterize recovery, and the operational definition of recovery itself. Standardization should therefore aim to make measurements interpretable and comparable across studies rather than assume that a single instrument can represent each domain across all populations and clinical settings.

In biological-age research, emphasis should shift from developing ever more clocks toward independent external validation of the most promising models. Most existing clinical aging clocks were developed in a single country, and a substantial proportion remain inadequately validated[29,32]. Clinical utility should be judged by incremental prediction and capacity to change decisions rather than by accuracy in reproducing chronological age.

Resilience research requires a transition from static assessment to repeated measurement around a health stressor. Elective surgery provides opportunities for standardized designs, while wearable technologies may

capture trajectories of mobility and activity between clinical encounters. Their value should be judged by the clinical interpretability of recovery patterns rather than by the volume of data collected.

Intervention studies should specify the domain being targeted a priori. Physical training may improve capacity, frailty, and function; environmental interventions may improve function with little effect on biology; and future geroscience interventions may alter biological markers without an immediate functional effect. Domain-specific outcomes may therefore improve interpretation of apparently discordant intervention effects.

Ultimately, the goal is not to identify a single best age measure but to determine the smallest set of complementary measurements that characterizes an individual's trajectory more accurately while remaining clinically feasible.

An additional priority is external validation of the framework across diverse ethnic, social, and clinical populations. Relationships among biology, capacity, vulnerability, response, and function may vary with access to health care, nutrition, disease patterns, and environmental conditions. The universality of the five-domain framework should therefore not be assumed; international prospective cohorts and harmonized outcome sets will be required.

Finally, development of another composite score would be premature. The initial objective should be to determine the independent and joint prognostic value of the domains, characterize their trajectories, and identify combinations that meaningfully alter clinical decisions. Formal operationalization of a multidimensional clinical aging phenotype should be considered only after these questions have been addressed.

Conclusion

Frailty is one of the most clinically important constructs in modern geriatrics and captures vulnerability to stressors within a broader multidimensional aging phenotype. Biological change, preserved capacities, vulnerability, capacity for recovery, and real-world functioning represent distinct, although interconnected, features of the aging individual. In the proposed framework, these features are represented by five domains: biology, capacity, vulnerability, response, and function. Biological age characterizes age-related biological change; intrinsic capacity, the physical and mental capacities available to the individual; frailty, vulnerability to stressors; resilience, the dynamics of response and recovery; and functional ability, functioning within the environment. The framework is not a new diagnostic scale and requires prospective validation. Its potential value lies in providing a common clinical architecture linking geroscience, frailty assessment, and functional geriatrics while enabling description of an individual's multidimensional clinical aging phenotype.

Author's Contributions

A.M.: conceived and designed the review, conducted the literature search, analyzed and interpreted the literature, developed the five-domain framework, drafted the manuscript, critically revised it for important intellectual content, approved the final version, and accepts responsibility for the integrity and accuracy of the literature analysis and synthesis.

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References

1. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. Lancet 2019;394(10206):1365-75.
2. Clegg A, Young J, Iliffe S, Olde Rikkert MGM, Rockwood K. Frailty in elderly people. Lancet 2013;381(9868):752-62.
3. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56(3):M146-56.
4. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci 2007;62(7):722-7.
5. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G. Untangling concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 2004;59(3):255-63.
6. World Health Organization. Integrated care for older people (ICOPE): guidance for person-centred assessment and pathways in primary care. 2nd ed. Geneva: World Health Organization; 2024.
7. Beard JR, Officer A, de Carvalho IA, Sadana R, Pot AM, Michel JP, et al. The World report on ageing and health: a policy framework for healthy ageing. Lancet 2016;387(10033):2145-54.
8. Cesari M, Araujo de Carvalho I, Thiyagarajan JA, Cooper C, Martin FC, Reginster JY, et al. Evidence for the domains supporting the construct of intrinsic capacity. J Gerontol A Biol Sci Med Sci 2018;73(12):1653-60.
9. Qi Y, van Schoor NM, Schaap LA, Hoogendijk EO. Disentangling the overlap between frailty and intrinsic capacity in older adults. Exp Gerontol 2026;213:113006.
10. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, et al. Geroscience: linking aging to chronic disease. Cell 2014;159(4):709-13.
11. 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;5(7):1207-16.
12. Fong S, Koh WP, Gruber J. Reframing biological age as risk-equivalent age. Nat Aging 2026;6(1):2-5.
13. Whitson HE, Duan-Porter W, Schmader KE, Morey MC, Cohen HJ, Colon-Emeric CS. Physical resilience in older adults: systematic

review and development of an emerging construct. J Gerontol A Biol Sci Med Sci 2016;71(4):489-95.
14. Dionyssiotis Y. Dysmobility syndrome, osteosarcopenia, and frailty: an ICF-based framework to differentiate function, tissue, and reserve. J Frailty Sarcopenia Falls 2026;11(1):1-3.
15. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. Res Integr Peer Rev 2019;4:5.
16. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc 2013;14(6):392-7.
17. Dent E, Morley JE, Cruz-Jentoft AJ, Woodhouse L, Rodriguez-Manas L, Fried LP, et al. Physical frailty: ICFSR international clinical practice guidelines for identification and management. J Nutr Health Aging 2019;23(9):771-87.
18. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173(5):489-95.
19. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci 2007;62(7):738-43.
20. Vermeiren S, Vella-Azzopardi R, Beckwee D, Habbig AK, Scafoglieri A, Jansen B, et al. Frailty and the prediction of negative health outcomes: a meta-analysis. J Am Med Dir Assoc 2016;17(12):1163.e1-1163.e17.
21. Kojima G. Frailty as a predictor of future falls among community-dwelling older people: a systematic review and meta-analysis. J Am Med Dir Assoc 2015;16(12):1027-33.
22. Kojima G. Frailty as a predictor of disabilities among community-dwelling older people: a systematic review and meta-analysis. Disabil Rehabil 2017;39(19):1897-908.
23. Kim DJ, Massa MS, Potter CM, Clarke R, Bennett DA. Systematic review of the utility of the frailty index and frailty phenotype to predict all-cause mortality in older people. Syst Rev 2022;11(1):187.
24. Kojima G, Taniguchi Y, Iliffe S, Jivraj S, Walters K. Transitions between frailty states among community-dwelling older people: a systematic review and meta-analysis. Ageing Res Rev 2019;50:81-8.
25. Rodriguez-Manas L, Feart C, Mann G, Vina J, Chatterji S, Chodzko-Zajko W, et al. Searching for an operational definition of frailty: a Delphi method based consensus statement: the Frailty Operative Definition-Consensus Conference Project. J Gerontol A Biol Sci Med Sci 2013;68(1):62-7.
26. Ferrucci L, Barzilai N, Belsky DW, Gladyshev VN. How to measure biological aging in humans. Nat Med 2025;31(4):1057.
27. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. Cell 2023;186(2):243-78.
28. Wyss-Coray T, Topol EJ. Biological aging clocks in health and disease. Nat Med 2026;32(7):2383-94.
29. 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.
30. Zalesky A, Wen J, Tian YE. From whole-body to organ-specific biological age clocks. Nat Aging 2026;6(5):961-9.
31. Oh HS, Rutledge J, Nachun D, Palovics R, Abiose O, Moran-Losada P, et al. Organ aging signatures in the plasma proteome track health and disease. Nature 2023;624(7990):164-72.
32. Zhang J, Hu J, Gao Y, Pang Z, Mo L, Wu IXY. Are aging clocks based on routine clinical indicators trustworthy and applicable? A systematic review and critical appraisal. J Gerontol A Biol Sci Med Sci 2026;81(4):glag032.
33. Tay JH, Barros D, Wang W, Wazny VK, Maier AB. Biological age measured by DNA methylation clocks and frailty: a systematic review and meta-analysis. Lancet Healthy Longev 2025;6(10):100773.
34. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol 2013;14(10):R115.
35. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat Rev Genet 2018;19(6):371-84.
36. Levine ME, Lu AT, Quach A, Chen BH, Assimes TL, Bandinelli S, et al. An epigenetic biomarker of aging for lifespan and healthspan. Aging (Albany NY) 2018;10(4):573-91.
37. Lu AT, Quach A, Wilson JG, Reiner AP, Aviv A, Raj K, et al. DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging (Albany NY) 2019;11(2):303-27.
38. Belsky DW, Caspi A, Corcoran DL, Sugden K, Poulton R, Arseneault L, et al. DunedinPACE, a DNA methylation biomarker of the pace of aging. Elife 2022;11:e73420.
39. Beard JR, Si Y, Liu Z, Chenoweth L, Hanewald K. Intrinsic capacity: validation of a new WHO concept for healthy aging in a longitudinal Chinese study. J Gerontol A Biol Sci Med Sci 2022;77(1):94-100.
40. Sanchez-Sanchez JL, Lu WH, Gallardo-Gomez D, Del Pozo Cruz B, de Souto Barreto P, Lucia A, et al. Association of intrinsic capacity with functional decline and mortality in older adults: a systematic review and meta-analysis of longitudinal studies. Lancet Healthy Longev 2024;5(7):e480-92.
41. Yu R, Lai ETC, Leung G, Ho SC, Woo J. Intrinsic capacity and 10-year mortality: findings from a cohort of older people. Exp Gerontol 2022;167:111926.
42. Cheng Y, Li W, Xiao S, Chen Y, Qi X. Intrinsic capacity and its dimensions in relation to functional ability in older adults: a systematic review and meta-analysis. Arch Gerontol Geriatr 2025;135:105860.
43. Belloni G, Cesari M. Frailty and intrinsic capacity: two distinct but related constructs. Front Med (Lausanne) 2019;6:133.
44. Chen X, He L, Shi K, Wen Q, Yu Q, Gao M, et al. Intrinsic capacity trajectories: implications for subsequent falls and hospitalizations among older adults. J Gerontol A Biol Sci Med Sci 2025;80(5):glaf017.
45. Hadley EC, Kuchel GA, Newman AB; Workshop Speakers and Participants. Report: NIA workshop on measures of physiologic resiliencies in human aging. J Gerontol A Biol Sci Med Sci 2017;72(7):980-90.
46. Varadhan R, Seplaki CL, Xue QL, Bandeen-Roche K, Fried LP. Stimulus-response paradigm for characterizing the loss of resilience in homeostatic regulation associated with frailty. Mech Ageing Dev 2008;129(11):666-70.
47. Walston J, Varadhan R, Xue QL, Buta B, Sieber F, Oni J, et al. A Study of Physical Resilience and Aging (SPRING): conceptual framework, rationale, and study design. J Am Geriatr Soc 2023;71(8):2393-405.
48. Colon-Emeric C, Schmader K, Cohen HJ, Morey M, Whitson H. Ageing and physical resilience after health stressors. Stress Health 2023;39(S1):48-54.
49. Whitson HE, Cohen HJ, Schmader KE, Morey MC, Kuchel GA, Colon-Emeric CS. Physical resilience: not simply the opposite of frailty. J Am Geriatr Soc 2018;66(8):1459-61.
50. Whitson HE, Ashner M, Kraus VB, Peskoe S, Huebner JL, Simon CB, et al. Comparing two methods to quantify physical resilience. J Frailty Aging 2026;15(4):100179.
51. Hu FW, Yueh FR, Fang TJ, Chang CM, Lin CY. Testing a conceptual model of physiologic reserve, intrinsic capacity, and physical resilience in hospitalized older patients: a structural equation modelling. Gerontology 2024;70(2):165-72.

52. Kolk D, Melis RJF, MacNeil-Vroomen JL, Buurman BM; Hospital-ADL Study Group. Physical resilience in daily functioning among acutely ill hospitalized older adults: the Hospital-ADL study. J Am Med Dir Assoc 2022;23(5):903.e1-903.e12.
53. World Health Organization. World report on ageing and health. Geneva: World Health Organization; 2015.
54. Govaerts J, Schaap LA, Timmermans EJ, Visser M, Huisman M, van Schoor NM. The association between intrinsic capacity and functional ability in older adults-exploring the role of the physical environment. Arch Gerontol Geriatr 2025;139:105999.
55. Cesari M, Canevelli M, Thiyagarajan JA, Arai H, Assantachai P, Chan P, et al. Frailty and intrinsic capacity: integrating complementary concepts to promote healthy ageing and transformation of care. Age Ageing 2026;55(5):afag138.
56. Bermejo Boixareu C, Martinez Velilla N, Neira Alvarez M, Abizanda Soler P, Alonso Bouzon C, Casas Herrero A, et al. Frailty prevalence and clinical outcomes according to assessment tools: a systematic review. Rev Esp Geriatr Gerontol 2026;61(4):101805.
57. Xu Y, Ji T, Li X, Yang Y, Zheng L, Qiu Y, et al. The effectiveness of the comprehensive geriatric assessment for older adults with frailty in hospital settings: a systematic review and meta-analysis. Int J Nurs Stud 2024;159:104849.
58. Ellis G, Gardner M, Tsiachristas A, Langhorne P, Burke O, Harwood RH, et al. Comprehensive geriatric assessment for older adults admitted to hospital. Cochrane Database Syst Rev 2017;9(9):CD006211.
59. Woo J. Frailty, successful aging, resilience, and intrinsic capacity: a cross-disciplinary discourse of the aging process. Curr Geriatr Rep 2019;8(2):67-71.
60. Chhetri JK, Xue QL, Ma L, Chan P, Varadhan R. Intrinsic capacity as a determinant of physical resilience in older adults. J Nutr Health Aging 2021;25(8):1006-11.
61. Hamaker M, Gijzel S, Rostoft S, van den Bos F. Intrinsic capacity and resilience: taking frailty to the next level. J Geriatr Oncol 2023;14(2):101421.
62. 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;3(12):1474-9.