Chapter 46: Frailty

Luigi Ferrucci; Elisa Fabbri; Jeremy D. Walston

This chapter addresses the following Geriatric Fellowship Curriculum Milestones: #21, #25, #72

LEARNING OBJECTIVES

Learning Objectives

- Gain perspective about the general concept of frailty in older persons.
- Understand alternative operational definitions of frailty.
- Recognize frailty in older persons.

Key Clinical Points

1. **Frailty is an important predictor of serious adverse outcomes, such as disability, health care utilization, and death. The phenotype of frailty includes the five following characteristics: unintentional weight loss, weakness, slow gait, exhaustion, and low activity. In addition there is a complex relationship between frailty and cognitive functioning.**
2. **Aging phenotypes that are closely related to frailty and late-life decline include (1) signalling networks that maintain homeostasis, (2) body composition, (3) balance between energy availability and energy demand, and (4) neurodegeneration/neuroplasticity.**
3. **A pervasive biological feature of aging and frailty is the presence of a chronic and mild proinflammatory state.**
4. **Multimorbidity is the clinical manifestation of frailty.**
5. **Frailty has become a key feature in evaluation of a number of specific medical conditions.**
6. **The paradigm of precision medicine provides an almost ideal entry for the frailty concept into the mainstream of modern medicine.**

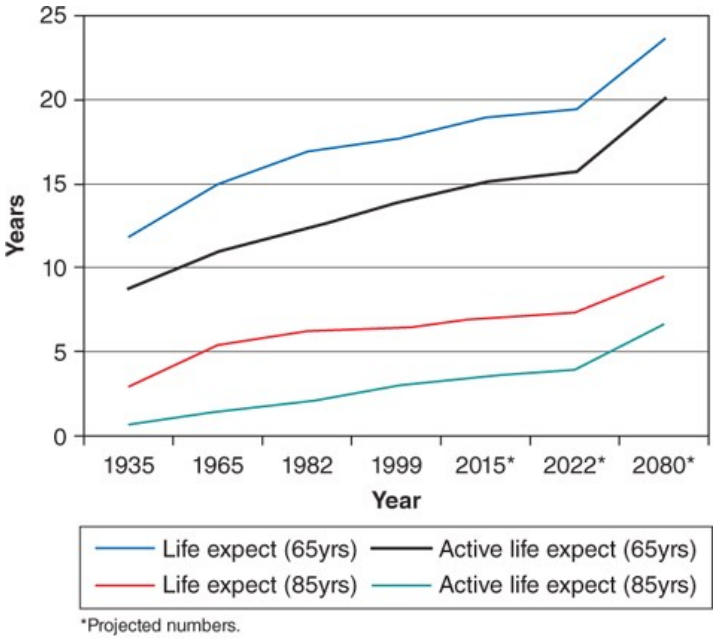
INTRODUCTION

Over the past century, the science of clinical medicine based on the identification of risk factors and pathophysiologic mechanisms of diseases has accomplished outstanding results. Since 1960, death rates for chronic diseases have changed dramatically, mainly as a consequence of smoking reduction and treatment of hyperlipidemia and hypertension. For example, heart disease death rates declined by almost two-thirds during the past 50 years, and stroke rates declined by more than three-quarters (http://www.cdc.gov). In spite of the relative success in performing early diagnosis, slowing down the clinical development and moderating the symptoms of many chronic diseases, the witnessed gain in longevity has helped to push

older adults into the part of life characterized by multimorbidity and disability, unfortunately with very little expansion of the period of life free from any illness (**Figure 46-1**).

Figure 46-1.

Life expectancy and active life expectancy at age 65 and 85, US population, 1935 to 2080, selected years (redesigned from published data). (Data from Manton KG, Gu X, Lamb VL. Long-term trends in life expectancy and active life expectancy in the United States. *Popul Dev Rev.* 2006;32(1):81–105.)



Geriatrics is the medical specialty that first perceived the limitations of traditional medicine: that a specific disease diagnosis or an assemblage of diagnoses could not encompass the substantial heterogeneity and complexity of the health problems presented by many older patients. Knowing the diseases and their clinical stage is not enough to explain presence and severity of physical and cognitive limitations. It has become more and more evident that the traditional biomedical principles that had been so effective in the care of patients with single disease were not similarly effective in the care of older patients. For geriatricians, understanding diseases is necessary but not sufficient to improve the health of their patients.

FROM COMPREHENSIVE GERIATRIC ASSESSMENT TO FRAILTY

The history of geriatric medicine has been focused on attempts to conceptually capture the complexity of older patients and develop standard tools for measuring it. This effort has demonstrated unequivocally that health status in older patients is best measured by the ability to function in the environment and that functional status provides powerful prognostic information on multiple adverse health outcomes independent of disease status. Consequently, one goal of geriatric medicine has been to elaborate a comprehensive care plan that would maximize functional status and quality of life of patients and their families. Progress in the field of functional assessment encompasses some of the most important research in the areas of clinical geriatrics and epidemiology of the last three decades. Self-report standard questionnaires were created and validated, followed by objective assessment of performance-based measures. An array of large epidemiologic studies provided robust evidence that even minor declines in physical function are associated with substantial deterioration of quality of life, are good metrics of disease severity, are more accurate and predictive than traditional organ-specific measures, and provide prognostic information for multiple health-related outcomes, including health care resources utilization, progression of disability, and mortality.

FRAILTY CONCEPTUAL DEVELOPMENT AND THE “LAYERS” OF FRAILTY

Most health care professionals recognize that there are complexities that are unique to geriatric patients. In spite of extensive research, the focus

described above on functional status and the development of functional assessment tools has failed to fill the vacuum of knowledge about the complexity of aging and its relationship with diseases and disability. Understanding physical and cognitive function is important, but does not provide clear and specific paths to interventions. Furthermore, since addressing each single disease did not require information on functional status, the assessment of functional status has often been left out of the clinical assessment.

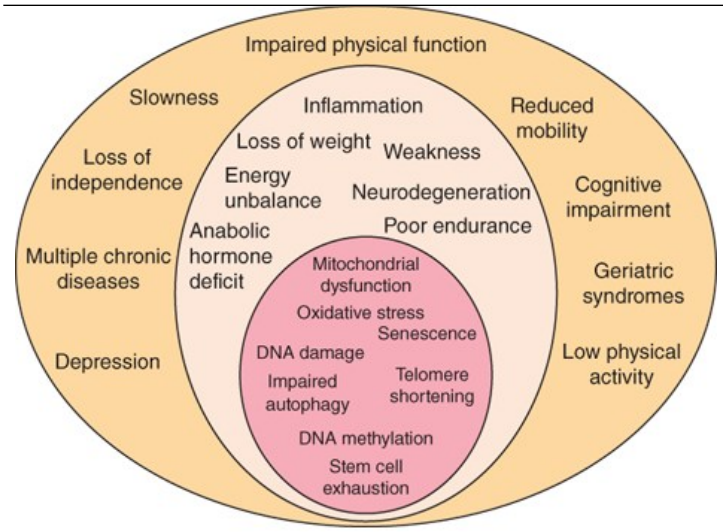
Overall, there is diffuse awareness that recognizing diseases is a necessary component of care, but it is often not enough to infer prognosis and fully understand health and functional status in older patients. The conceptualization and operationalization of frailty is an attempt to capture the missing components of deteriorating health status that are often overlooked in the traditional medical approach.

While creating a standard definition of frailty is a daunting task, it is often argued that most geriatricians can easily recognize frail older persons when they see and interact with them. This hypothesis was examined by a formal multistage Delphi process conducted between 2011 and 2012 that asked a large number of geriatricians, health care providers, and experts to identify the critical characteristics that define a frail older person. Not unexpectedly, results were mixed. The majority of participants agreed that frailty should be considered a clinical syndrome that involves multiple physiologic systems, characterized by decreased reserve and impaired ability to respond to stress, and useful in different settings to identify individuals at high risk of developing adverse health outcomes. However, there was very little agreement on a specific set of clinical/laboratory biomarkers useful for diagnosis. Because of the lack of clarity and the need to determine whether there was sufficient information available to justify systematic screening for frailty, a consensus conference was convened in Orlando, Florida, on December 7, 2012. The project was endorsed by experts from six major international scientific societies and included the participation of other independent top experts in the field. Consistent with the previous experience, a construct of frailty emerged as a “medical syndrome with multiple causes and contributors characterized by diminished strength, endurance, and reduced physiologic function that increases an individual’s vulnerability for developing increased dependency and/or death” (Morley et al., 2013). There was consensus that because frailty screening is particularly important to identify individuals at risk of disability, the definitions of frailty and disability should not overlap and that frailty cannot be exhaustively defined by the presence of sarcopenia or multimorbidity. The published report from the conference supported screening for frailty in all individuals 70 and older using some of the operational criteria developed and validated. However, the rationale provided in support of population screening was less than robust. In fact, while frailty can be prevented (eg, by regular exercise) and even partially reversed (possibly by vitamin D or simplification of polypharmacy), so far no randomized controlled trial has definitively demonstrated that screening older individuals for frailty is associated with significant benefits. In addition, there are not specific clinical guidelines available on how frail older adults might be managed differently. However, as described later in this chapter, there is evidence supporting screening of specific subgroups and indicating the need for more research in this area.

Starting from the conclusions of the consensus documents reported earlier, the complexity of typical frail patients can be conceptualized by considering their features in concentric layers, like the layers of an onion (**Figure 46-2**).

Figure 46-2.

Frailty can be conceptualized as a construct with three overlaying dimensions, similar to layers of an onion. The clinical presentation, including cognitive and physical impairments, is in the first, most superficial layer. The second layer includes a number of hypothetical pathophysiologic mechanisms and can also be considered as the “area of biomarkers.” The third, most inner layer includes the biological mechanisms that are hypothesized to be primary causes of frailty. (From Ferrucci and Fabbri, unpublished data.)



The first layer is the clinical presentation characterized by *multimorbidity*, *impaired physical function* (including mobility), and *cognitive impairment*. These characteristics can be considered as the common beacon at the confluence of all frailty characteristics that contribute to the clinical syndrome. The clinical elements in this layer convey most of the prognostic information for disability, mortality, and many other adverse health outcomes. Examples are *walking speed*, *lower extremity performance*, *reduced physical activity*, *poor muscle strength*, *poor memory*, *number of diseases*, *number of drug treatments*, and many others. Part of this first layer is also a dynamic dimension that is clinically observable, characterized by *reduced functional reserve*, *impaired resilience* to a number of stresses, and *delayed and incomplete recovery* after homeostatic perturbations, health instability, and impending deterioration of health and functional status.

Older patients who come to the observation of geriatricians often present these characteristics and show a spiral of progressive health deterioration in spite of medical treatment aimed at promoting recovery and stabilization (**Table 46-1**). Often these patients develop one or more "geriatric syndromes," common clinical conditions that do not fit into specific disease categories but have substantial implications for functionality and life satisfaction in older adults. Conditions most commonly considered geriatric syndromes are pressure ulcers, incontinence, falls, gait problems, delirium, malnutrition, sleeping problems, dizziness, syncope, and self-neglect. In describing the main physiologic changes that occur with aging, we will come back to this point and explain how it can be quite useful to consider the geriatric syndromes as an overt manifestation of different combinations of the aging phenotypes.

TABLE 46-1

CHARACTERISTICS OF FRAILTY

Increased vulnerability
Reduced physiologic reserves
Decreased resistance to stressors
Reduced capacity to maintain internal homeostasis
Loss of resilience
Multisystem dysregulation
Failure to thrive
Accumulation of deficits
Functional decline
Dependence in daily activities
Impaired mobility
Disability
Comorbidity
Cognitive impairment
Poor health function
Poor psychological functioning
Depression
Unintentional weight loss
Sarcopenia/muscle wasting
Weakness
Low strength
Slow motor performance
Slow walking speed
Decreased balance
Low energy expenditure
Low physical activity
Low fitness
Poor endurance
Exhaustion
Gait abnormality
Impaired vibration sense tremor
Vision and/or hearing deficits

The next, second layer closer to the frailty core could be defined as the “area of biomarkers,” and departs from a purely descriptive interpretation of frailty by providing some information on possible mechanisms. Research on frailty has pointed to multisystem impairments across multiple physiologic systems and organs: (1) Muscle mass and strength are reduced and fat mass increased over and beyond what is expected from the pure effect of aging, and these changes are accompanied by extreme bone fragility; (2) level of fitness is poor and accompanied by altered resting metabolic rate and reduced energetic efficiency, which likely contribute to fatigue and reduced mobility; (3) some homeostatic mechanisms are impaired, show low reserve and reduced ability to respond to perturbation, and have reduced ability to recover a stable level of equilibrium. Examples include the hypothalamic-pituitary-adrenal (HPA) axis cortisol response to stress or the homeostatic response after an oral load of carbohydrates. Perhaps the most pervasive homeostatic dysregulation feature of aging is the acquisition of a proinflammatory state, demonstrated by chronically elevated levels of cytokines and associated with blunted immune response to vaccination and/or to infection, which lead to predisposition to infections. Kidney function is substantially impaired beyond what is expected by aging. Anemia and malnutrition are also almost constant features of aging and frailty. The three main portions of the nervous system (central, peripheral, and autonomic) likely have some degree of involvement and play an important role in the physical and cognitive manifestations of frailty. Imaging studies show that frailty is associated with leukoaraiosis as well as presence of micro-

and macroischemic lesions in the white matter, longer reaction time, and reduced performance in dual tasks that involve both cognitive and physical challenges.There is motor neuron loss and fragmentation of the neuromuscular junction, which probably contributes to sarcopenia and poor mobility. Impaired orthostatic hemodynamics, heart rate control, and reduced intestinal peristalsis are signs of autonomic dysfunction. While many studies have considered relationships of frailty with single physiologic and pathologic features, the constant involvement of multiple physiologic systems in frailty suggests that most of them are driven by some unifying cause, although still unknown and hidden.

In parallel to the conceptual development of frailty as a clinical entity with profound functional consequences and poor prognosis, its biological basis is being investigated. The biological basis of frailty represents the deeper, third layer of the onion-like frailty syndrome model, which is purely mechanistic and still largely hypothetical. Attempts to understand the core mechanisms of frailty provide the basis for making a connection between the biology of aging and the experience of geriatric practice. Some hypothesize that aging and frailty are manifestations of the same biological mechanisms, and that frailty is in fact “accelerated aging.” This is consistent with the idea that aging affects resilience, the susceptibility to any stressful event that perturbates the homeostatic equilibrium essential for life and impairs the chances of regaining the lost equilibrium. The accumulation of damage due to loss of resilience across different physiologic systems leads to multimorbidity, the development of the aging phenotype, and decline in many functions that ultimately impact physical and cognitive performance, triggering events that eventually lead to death. Of course, if frailty and aging are made of the same fabric, then understanding the biological mechanisms of frailty may inform our understanding of aging.

FROM SPECULATION TO PRACTICE: OPERATIONAL DEFINITIONS OF FRAILTY

The concept of frailty emerged as a logical extension of comprehensive geriatric assessment, as an attempt to reconstitute clinical and research perspectives under a unique umbrella.

As opposed to functional assessment, which attempts to assess and track the consequence of the physiologic decline that occurs with aging and tries to characterize its consequences regardless of its causes, the concept of frailty implies the existence of underlying pathophysiologic mechanisms responsible for the phenotypical manifestations of aging. Although different interpretative frameworks for frailty have been developed, with different operational criteria, all of them connect frailty directly or indirectly with the biology of aging.

FRAILTY AS A SYNDROME OR PHENOTYPE

The operational model of frailty developed by Linda Fried and other investigators working in the Cardiovascular Health Study (CHS) is supported by a large body of strong methodological work. According to these authors, frailty is a dysregulation of the stress response systems responsible for organismal resilience, leading to loss of homeostatic capabilities, increased susceptibility to stress, and the emergence of a distinct syndromic phenotype that is predictive of a range of clinical adverse outcomes. The syndromic attribution to frailty in CHS was later validated by research conducted on the Women’s Health and Aging Study, and implies that the criteria used for the clinical definition are not exhaustive of the syndrome but rather represent biomarkers that in the aggregate allow for the identification of a group of subjects likely to be affected by the syndrome with some level of sensitivity and specificity.

In describing their theoretical construct of frailty, the authors consider the diagnostic criteria as the milestones of a pathologic vicious cycle that lead to a progressive decline in health and function. The visual representation of this cycle is now part of the background culture in geriatrics and gerontology (**Figure 46-3**). Subsequent models from the same research group have helped to facilitate the testing of biological hypotheses related to frailty and other adverse health outcomes often observed in older adults (**Figure 46-4**). This evolution toward a deeper biological and etiologic understanding is key to progress in this field.

Figure 46-3.

Schematic representation of the pathologic vicious cycle supposed to lead to a progressive decline in health and function according to the Linda Fried model. (From Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):M146–M156.)

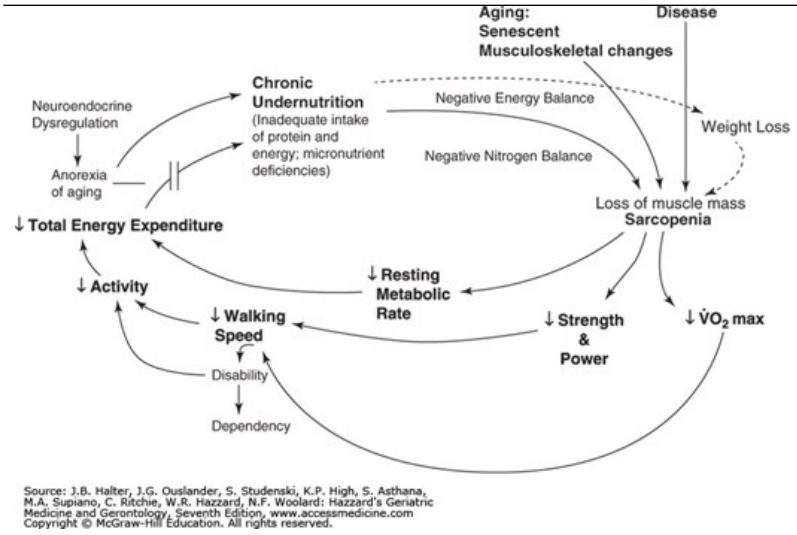
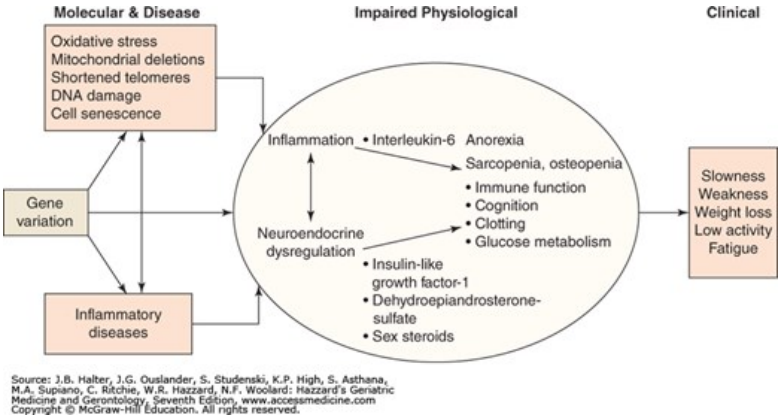


Figure 46-4.

An updated version of the frailty model presented in **Figure 46-3**, subsequently proposed by Linda Fried and Jeremy Walston. (From Walston J, Hadley EC, Ferrucci L, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc*. 2006;54(6):991–1001.)



Based on the clinical observation that frail older individuals often have low lean body mass; poor strength, balance, and walking performance; and low physical activity, Fried and colleagues conceptualized frailty as a vicious circle of declining energetics and reserve, whose elements represent both the diagnostic criteria for the syndrome identification and the core elements of its pathophysiology. In particular, the phenotype of frailty was defined by the five following characteristics (**Table 46-2**): unintentional weight loss, weakness, exhaustion, slowness, and low activity.

TABLE 46-2

CRITERIA FOR FRAILTY SYNDROME ACCORDING TO FRIED AND COLLEAGUES

CHARACTERISTICS OF FRAILTY	CARDIOVASCULAR HEALTH STUDY MEASURE
1. Weight loss (unintentional)/sarcopenia (loss of muscle mass)	> 10 lb lost unintentionally in prior year
2. Weakness	Grip strength: lowest 20% (by gender, body mass index)
3. Exhaustion/poor endurance	"Exhaustion" (self-report)
4. Slowness	Walking time/15 ft: slowest 20% (by gender, height)
5. Low activity	kcal/wk: lowest 20% males: <383 kcal/wk; females: < 270 kcal/wk

Adapted from Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146 -M156.

Those individuals who meet at least three of the five criteria are considered frail, while those individuals who meet two criteria out of five are considered as prefrail. Of note, the presence of one criterion alone may constitute a risk factor but does not represent frailty itself, because frailty is considered a multisystemic syndrome. Using this operational definition, the severity of frailty is associated with risk for disability and loss of independence, even in the absence of an acute precipitant. In addition, frailty is associated with the presence of specific chronic diseases, particularly those with an inflammatory etiology, and patients with chronic multimorbidity are likely to be frail or have high risk of developing frailty. While frailty incidence rises with increasing age independent of chronic diseases, the association with such chronic diseases, including cardiovascular, kidney, and rheumatologic diseases, suggests that there may be both a primary, aging-related frailty and a phenotype of frailty that is secondary to chronic disease or jointly related to a shared etiology.

The Fried approach to frailty is appealing because it is both easy and immediate to operationalize and also is based on a solid pathophysiologic model that directly indicates opportunities for interventions. However, this approach of frailty also has few drawbacks. The first problem is the lack of a cognitive dimension, which is in contrast with the clinical experience that cognitive impairment often accompanies frailty. Brain dysfunction can be captured by the mobility assessment but still patients in the early stage of frailty who develop mostly cognitive manifestations may be missed. A second problem is the inclusion of weight loss in the syndrome. Unexplained weight loss is a strong biomarker of health decline with aging. However, given the increasing prevalence of obesity, the sarcopenic-obesity variant of frailty is becoming more and more frequent, and this variant may be missed by the weight loss criterion. Third, the threshold selected for the definition of some of the criteria are based on distributions in the CHS population, which may not be fully representative of all clinical populations in the United States. In spite of these limitations, an extensive literature demonstrates that the Fried definition of frailty is a useful tool both for research and clinical applications, and it has been adapted to many studies and uses. Examples of the many successful applications are given later in this chapter.

FRAILTY AS A DEFICIT ACCUMULATION

Another major school of thought that has been a mainstream in frailty research is the approach developed by Ken Rockwood and colleagues. In this approach, frailty is considered an accumulation of illnesses, signs, symptoms, and laboratory abnormalities, based on the observation that "the more things individuals have wrong with them, the higher the likelihood that they will be frail". Using data from two population-based Canadian studies, Rockwood and his collaborators combined a series of 70 measurements (jointly referred to as "deficits") in order to generate a multisystem, broad, graded, and conceptually simple tool into the frailty index (FI). This approach conceptualizes frailty as a stochastic accumulation of structural and functional deficits in almost any physiologic system or organ and operationalizes it as a simple unweighted count of the number of deficits. The FI, in particular, is the ratio of the deficits present in a person to the total number of deficits considered. Therefore, according to this definition, it is the proportion of all potential deficits considered for a given person rather than their specific nature or combination that best expresses the likelihood and the severity of frailty. The FI and multiple shorter versions of the original FI have most often been used as a means of assessing individual aging and risk of mortality as described below.

In building their model of frailty, Rockwood and his colleagues used data from the Canadian Study of Health and Aging (CSHA) and followed three subsequent approaches. First, they developed a rules-based definition of frailty, followed by a method of counting 70 of a patient's various clinical deficits. Items consisted of the presence and/or severity of current diseases, ability in activities of daily living (ADLs), and physical signs from the clinical and neurologic examinations. Each deficit was dichotomized or trichotomized and mapped to the interval 0 to 1, representing the occurrence and severity of the problem. The FI has a strong face validity; it shows an age-specific, nonlinear increase (similar to Gompertz law), higher values in females, strong associations with adverse outcomes (eg, mortality), and a universal limit to its increase (at FI ~ 0.7). The authors interpreted these findings as a proof that FI tracks rate of individual aging. This approach is reproducible and highly correlates with mortality, but it is unwieldy for clinical use. Therefore, more recently, Rockwood and collaborators developed a third approach, based on the determination and validation of a seven-category tool, named the Clinical Frailty Scale, which is easier to use in clinical settings and has similar predictive power for institutionalization and death. The seven categories of the Clinical Frailty Scale are (1) very fit, (2) well, (3) well with treated comorbid disease, (4) apparently vulnerable, (5) mildly frail, (6) moderately frail, and (7) severely frail. The Clinical Frailty Scale mixes items such as comorbidity, cognitive impairment, and disability that some other groups separate in focusing on physical frailty.

The FI approach has several attractive features but some drawbacks as well. First, as a prognostic tool, the FI is a sensitive predictor of adverse health outcomes, in part because it includes multiple related factors known to share causal relationships with adverse outcomes. The clinical version of the tool is very direct and intuitive, has strong face validity, and shorter versions of FI can be generated quickly from medical records. The stochastic approach of the FI approximates the idea of aging as a rise in entropy, which makes intuitive sense and is supported by a wealth of research data and solid mathematical models. On the other hand, a pure stochastic approach is inconsistent with the idea of a specific "hub" biological mechanism that causes frailty. This and the lack of a focused list of measures make the development of specific mechanistic, biological, and intervention development studies needed to move toward focused clinical strategies more challenging. Finally, the FI, even with multilevel variables, is still based on the assumption of equality of deficits. It would be of interest to differently weight the variables to have greater influence at predicting the adverse outcomes.

OTHER OPERATIONAL DEFINITIONS OF FRAILTY

There are many other operational definitions of frailty beyond the two described above, although most of them arise from the already discussed concepts. The most relevant operational definitions are summarized in **Table 46-3**. The wide variety and number of published tools document the very lively discussion in the field about the definition and interpretation of frailty, which has occupied many hours in meetings, workshops, and roundtables, at times louder and more emotional than one would have liked.

TABLE 46-3

SUMMARY OF THE FRAILTY TOOLS PUBLISHED IN THE LITERATURE

INSTRUMENT	PUBLICATION(S)	DOMAINS/ITEMS	SCORING
Physical Frailty Phenotype (PFP)	Fried et al., *J Gerontol*, 2001	Physical function (gait speed, grip strength), physical activity, weight loss, and exhaustion	Score range: 0–5 Frail = ≥ 3 criteria present Intermediate/prefrail = 1–2 criteria present Robust/nonfrail = 0 criteria present
Deficit Accumulation Index (DAI)	Mitnitski et al., *The Scientific World*, 2001;Mitnitski et al., *J Gerontol Med Sci*, 2004; Rockwood et al., *J*	Diseases, activities of daily living (ADL), health attitudes/values, and symptoms/signs from clinical and neurologic examinations	Number of deficits present and divided by the number of deficits taken into consideration Higher proportion

	Am Geriatr Soc, 2006; Rockwood et al., *J Gerontol Med Sci*, 2007a; Rockwood et al., *J Gerontol Med Sci*, 2007b		equates to a higher level of frailty Number of deficits may vary
Gill Frailty Measure	Gill et al., *N Engl J Med*, 2002	Physical function (gait speed, chair stand)	Moderately frail if rapid gait speed back and forth over 10 ft course is > 10 s; or could not stand from the chair. Severely frail if meet both criteria
Frailty/Vigor Assessment	Speechley & Tinetti, *J Am Geriatr Soc*, 1991	Frail: age (over 80), physical function (balance and gait abnormalities, decreased shoulder strength, decrease knee strength), physical activity (infrequent walking for exercise); psychological function (depressed); medications (taking sedatives); disability (lower extremity disability); sensory function (near vision loss). Vigorous: age (under 80), cognition (cognitively intact), physical activity (frequent exercise other than walking), sensory function (good near vision)	Score ranges: Frail 0–9 Vigorous 0–4 Frail: ≥ 4 frail values and ≤ 1 vigor value Vigorous: ≥ 3 vigor values and ≤ 2 frail values Transitional: having median values for either or both frail (3) and vigor (2)
Clinical Frailty Scale	Rockwood et al., *CMAJ*, 2005	Clinical judgment from very fit to severely frail: 1 = Very fit—robust, active, energetic, well motivated, and fit; these people commonly exercise regularly and are in the most fit group for their age; 2 = Well—without active disease, but less fit than people in category 1; 3 = Well, with treated comorbid disease—disease symptoms are well controlled compared with those in category 4; 4 = Apparently vulnerable—although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms; 5 = Mildly frail—with limited dependence on others for instrumental activities of daily living; 6 = Moderately frail—help is needed with both instrumental and noninstrumental activities of daily living; 7 = Severely frail—completely dependent on others for the activities of daily living, or terminally ill	Physician assigns score of 1–7 based on clinical judgment Physicians making the initial assessment given access to diagnoses and assessments related to these variables and other measures of comorbidity, function, and associated features that inform clinical judgments about the severity of frailty A secondary review and scoring performed by a multidisciplinary team

Brief Frailty Instrument	Rockwood et al., *Lancet*, 1999	Four levels of classification, representing fitness to frailty: 0 = Those who walk without help, perform basic activities of daily living (eating, dressing, bathing, bed transfers), are continent of bowel and bladder, and are not cognitively impaired 1 = Bladder incontinence only 2 = One (two if incontinent) or more of needing assistance with mobility or activities of daily living, has cognitive impairment with no dementia (CIND), or has bowel or bladder incontinence 3 = Two (three if incontinent) or more of totally dependent for transfers or one or more activities of daily life, incontinent of bowel and bladder, and diagnosis of dementia	Higher classification means higher grade of frailty
Vulnerable Elders Survey (VES-13)	Saliba et al., *J Am Geriatr Soc*, 2001	Age, self-rated health, physical function, and ADL/IADL disability	Score range: 0–10 Frail = score ≥ 3
FRAIL Scale	Abellan Van Kan, *J Nutr Health Aging*, 2008; Abellan Van Kan, *J Am Med Dir Assoc*, 2008	Fatigue, physical function (resistance: ability to climb a single flight of stairs; and ambulation: ability to walk one block), illnesses (more than 5), weight loss (more than 5%)	Score range 0–5 No frailty = 0 deficits Intermediate frailty = 1 or 2 deficits Frailty = 3 or more deficits
Winograd Screening Instrument	Winograd et al., *J Am Geriatr Soc*, 1991	Cerebrovascular accident; chronic and disabling illness; confusion; dependence in ADLs; depression; falls; impaired mobility; incontinence; malnutrition; polypharmacy; pressure sore; prolonged bed rest; restraints; sensory impairment; socioeconomic/family problems	Frail = presence of any *one* of the 15 screening criteria Participants could instead be categorized as “severely impaired” if they had severe dementia *and* ADL dependence, or terminal illness

Adapted from Buta BJ, Walston JD, Godino JG, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments, Ageing Res Rev. 2016;26:53-61.

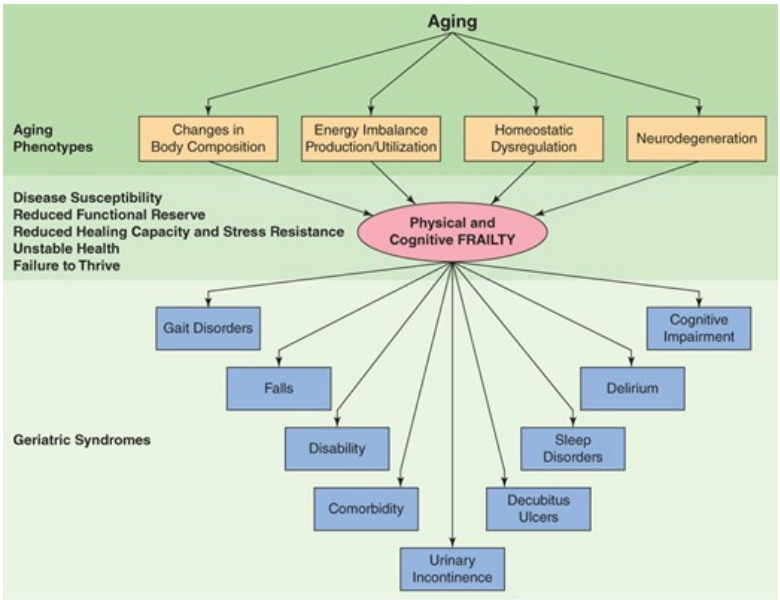
A NOVEL APPROACH: FRAILTY AS AGE-RELATED BIOLOGICAL DECLINE

Recently, we and others proposed that while agreeing on an operational definition of frailty is very important for translational purpose, until the pathophysiology of frailty is fully understood, any operational definition of frailty should be considered temporary and amenable to change. Importantly, the theoretical discussion and research on the biological and mechanistic origin of frailty does not completely depend on a specific operational definition. We recently proposed an agnostic approach, which assumes that frailty is, in fact, a syndrome of accelerated aging and, therefore, phenotypes of aging as well as frailty can be identified as those physiologic dimensions that change with aging in all humans and, perhaps, in all living organisms. For example, the risk of developing a clinical disease such as coronary artery disease (CAD) increases with aging but not all individuals develop CAD. Therefore, CAD cannot be considered a phenotype of aging. On the other hand, percent body fat, especially visceral fat, increases with aging in all individuals and, therefore, increased visceral fat could be considered a phenotype of aging. Based on these assumptions, we proposed that the phenotypes of aging can be clustered in discrete interactive domains, whose impairments are pervasive across body systems and,

therefore, can serve as proxy measures of the rate of aging. In particular, we identified four main "aging phenotypes" that we hypothesize are closely related to frailty and late-life decline: (1) signalling networks that maintain homeostasis; (2) body composition; (3) balance between energy availability and energy demand; and (4) neurodegeneration/neuroplasticity, whose changes occur in parallel in all aging individuals and are strongly intercorrelated (**Figure 46-5**). Extensive evidence, in fact, shows that frailty is associated with overt changes in these four main interacting domains regardless of its operational definition. Such conceptualization of frailty also recognizes the heterogeneity and dynamic nature of the aging process. Aging is a universal phenomenon, but the progressive multisystem instability and deterioration that characterize aging are very heterogeneous among different individuals. Thus, not only whether an older patient is frail, but also whether the severity of the frailty syndrome is beyond clinical and behavioral thresholds becomes relevant. Furthermore, the conceptualization of frailty as a result of various levels of impairment in the "aging phenotypes" represents an interconnecting and dynamic interface between the clinical presentation of the syndrome (first layer of frailty) (see **Figure 46-2**) and its biological bases (the inner and deeper layer or biological core of frailty). This model provides a causal link to the development of multiple chronic diseases and geriatric syndromes, whose occurrence can be interpreted as clinical expression of alterations in specific combinations of aging phenotypes.

Figure 46-5.

Schematic representation of the domains of the aging phenotype, and their relationship with frailty and with the geriatric syndrome. (From Ferrucci L, Studenski S. Clinical problems of aging. In: Longo DL, Fauci AS, Kasper DL, et al., eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York, NY: McGraw Hill; 2012.)



Signalling Networks That Maintain Homeostasis

A remarkable and pervasive biological feature of aging and frailty is the presence of a chronic and mild proinflammatory state, revealed by elevated levels of serum proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α). Such a proinflammatory signature of aging, also called "inflammaging," has been described across different animal models and tissues, and is even present in individuals who are free of diseases, disabilities, and cardiovascular risk factors (Ferrucci et al., 2005). Moreover, higher levels of proinflammatory biomarkers have been associated with loss of physiologic reserve and function across multiple organs and system in older adults. These biomarkers are strong independent predictors of adverse health outcomes including multiple chronic diseases, disability, hospitalization, and mortality.

Research on the biology of aging has shed some light on the underlying mechanisms of the proinflammatory state of aging. For example, one of the possible triggers is defective autophagy, a fundamental cellular housekeeping mechanism that eliminates altered macromolecules, cell membranes, and organelles before they are replaced. In particular, the processing and elimination of aged and degraded mitochondria appears to be impaired. These dysfunctional mitochondria cannot be replaced, are energy inefficient, and produce large quantities of radical oxygen species which are

supposed to trigger a chronic inflammatory response. Animal models demonstrate a strong connection between the accumulation of senescent cells and the development of characteristic aging phenotypes. One of the main features of senescence is the senescence-associated secretory phenotype that is characterized by the secretion of proinflammatory mediators, including IL-6 and IL-1, and may account for the proinflammatory state of aging.

An additional and relevant characteristic of the aging process is the occurrence of complex and profound hormonal changes, including a decline in multiple anabolic hormone concentrations (dehydroepiandrosterone sulfate [DHEAS], testosterone, estrogens, growth hormone [GH]/insulin-like growth factor 1 [IGF-1], and vitamin D), with a relative preservation of catabolic hormones (thyroid hormones, cortisol). A single hormonal alteration, in fact, is unusual in older persons and usually is a sign of a specific impending disease. More often, aging individuals experience a complex "multiple hormonal dysregulation," characterized by simultaneous and synergistic mild multiple anabolic hormonal deficiencies, which may be an important contributor to progressive loss of resilience and high vulnerability in older adults. Multihormonal dysregulation has also been associated with the development of numerous geriatric conditions, including sarcopenia and cognitive decline as well as high risk of disability, comorbidity, and mortality.

Body Composition

Aging is also characterized by major changes in body composition which negatively affect metabolism and functional status. These changes contribute to impaired mobility, disability, and other adverse health outcomes in older adults. Lean body mass, composed predominantly of muscle and visceral organs, starts to decline progressively around the age of 30 with a more accelerated loss after the age of 60, while fat mass increases with age during middle age and declines in late life. Age-related loss of muscle mass is typically offset by gains in fat mass as adults age with resulting stable or slightly increasing body weight. After the age of 70, fat-free mass and fat mass tend to decrease in parallel, with consequent decreasing weight. Furthermore, visceral fat and intermuscular fat tend to increase with age, while subcutaneous fat in other regions of the body declines. The age-related loss of muscle mass, with a shift in muscle fiber composition, due to a selective loss in fast-twitch fibers compared to slow-twitch fibers, was long considered the major determinant of decline in muscle strength in older adults.

However, the decrease in muscle strength actually exceeds what is expected on the basis of the decline in muscle mass alone, especially after the age of 60 to 70, suggesting that other factors related to muscle quality (defined as muscle strength or power per unit of muscle mass) may play a major role in the decline in muscle strength and physical function in older adults. Muscle biomechanical quality, defined at the force that is generated by a volume unit of muscle tissue, is almost constant in children and young adults but starts deteriorating after the age of 40. Progressive muscle denervation secondary to progressive failure of the denervation/reinnervation cycle and to dysfunction of the neuromuscular junction is probably largely responsible for the decline of muscle mass and quality with aging. Furthermore, there is increased fat infiltration within the muscle, which probably results from age-related changes in body composition and includes storage of lipids in adipocytes located between the muscle fibers (also termed intramuscular fat) and between muscle groups (intermuscular fat) as well as lipids stored within the muscle cells themselves (intramyocellular lipids). This fat infiltration is thought to be largely responsible for the deterioration of muscle quality, impaired muscle force production, and mobility decline in older adults.

In addition, an increase of fibroconnective tissue within the muscle contributes to poor muscle quality with aging. Another focus is on the failure of mechanisms of the maintenance and repair of damaged muscle fibers, mainly due to the limited regenerative capacity and dysfunction of satellite cells (stem cells resident in muscle tissue), which may be exhausted before the end of life in situations that require continued and intensive repair. Overall, the decline in muscle mass and muscle strength with aging plays a critical role in the development of the frailty syndrome.

Progressive demineralization and architectural modification in the bone also occurs with aging, with consequent increased skeletal fragility and higher risk of fractures, especially at the hip. Trabecular bone mass "peaks" in early adult life, with decreases in trabecular bone evident in both sexes as early as the third decade, although the rate of decline is clearly accelerated in women compared to men.

Balance Between Energy Availability and Energy Demand

Although the idea that longevity and health are linked to energy metabolism was introduced over a century ago, the role of energy metabolism in human aging and chronic diseases is still not fully understood. As described earlier, Fried and colleagues conceptualized frailty as a vicious cycle of declining energetics and reserves. Indeed, the integrity of energetic metabolism is a prerogative for successful aging. In fact, the degenerative processes that characterize aging occur when the organism's ability to balance energy production and expenditure declines. Lack of energy or even an excess of energy that is not utilized could be the root causes of progressively higher morbidity and mortality with aging. Resting metabolic rate (RMR) is the energy required to maintain structural and functional homeostasis at physical rest, in fasting and neutral conditions. RMR accounts for 60% to 70%

of the total daily energy expenditure and can be assessed by indirect calorimetry. RMR normalized by body size declines rapidly from birth up to the end of the third decade, and then continues to decline more slowly from adulthood until death, mostly but not completely, as a consequence of the age-related loss of lean body mass.

In older adults higher RMR has been found to be an independent risk factor for mortality and to predict future greater burden of chronic diseases; consequently it should be considered a marker of health deterioration in older adults. Specifically, the increased RMR is likely to be due to increasing difficulties to cope efficiently and effectively with internal and environmental challenges and stressors. Therefore, in the presence of overt homeostatic dysregulation, the energy requirement increases because of the extra work required to maintain a stable homeostasis.

Moreover, the maximum energy that can be produced by an organism over extended time periods, or fitness, can be approximately estimated during a maximal treadmill test as peak oxygen consumption (VO_2 max). Oxygen consumption represents the maximal ability to use oxygen to meet the energy demands of physical activity (maximal aerobic capacity) and reflects not only cardiovascular adaption to transport oxygen but also adaptations within muscle to use oxygen to meet the energy demands of physical activity. VO_2 max declines with age, starting around age 30 and continuing at approximately 10% per decade, but at an accelerated rate for increasing age and in those who are sedentary or affected by chronic diseases. Of relevance, the age-related decline in maximal aerobic capacity is a strong predictor of decline in physical function and mobility in older adults.

Neurodegeneration

An important biomarker of aging and frailty is the age-related degeneration of the central and peripheral nervous system (for details see Chapter 45). As result of these changes, declining performance in specific cognitive abilities, like memory, processing speed, executive function, reasoning, and multitasking is commonly experienced with aging. All of these so-called “fluid” mental abilities are important for carrying out everyday activities, living independently and leading a fulfilling life. In fact, there is a strong association between accelerated decline in cognitive performance and in mobility, even in “normal” older adults.

Age-related changes occur also at the level of the peripheral nervous system (PNS), especially after the age of 60, with a progressive degeneration in structure and function from the spinal cord motor neuron to the neuromuscular junction. These changes in the PNS greatly contribute to impaired mobility and decline in physical function in older adults. The number of motor neurons declines with aging and such declines seem to play an important role in the loss of muscle strength and quality with aging. Age-related motor unit remodeling leads to changes in fiber-type composition because denervation occurs preferentially in the fast muscle fibers with reinnervation occurring by axonal sprouting from slow fibers. As a consequence, motor units decrease in number and become progressively larger, but less functional with aging with reductions in fine motor control. Furthermore, the efficiency of segmental demyelination-remyelination process declines with aging, resulting in slower conduction of the impulses, with consequent decreased sensation as well as slower reflexes.

THE EPIDEMIOLOGY OF FRAILTY

The prevalence of frailty varies enormously among studies according to different definitions, countries, and settings. A systematic review reported that the overall prevalence of frailty, in community-dwelling adults aged 65 and older, is on average 10.7% (range 4.0%–59.1%). Of note, use of a broader definition of frailty results in a higher prevalence than use of the Fried tool (13.6% vs 9.9%). Moreover, prevalence of frailty increases with age, reaching 15.7% in individuals aged 80 to 84 and 26.1% in those aged 85 or more. Independent of the type of definition, the prevalence is higher in women than men (Fried Scale: 9.6% vs 5.2%; FI: 39.0% vs 37.3%). Also, frailty, however defined, shows a U-shaped relationship with body mass index (BMI), with higher levels of frailty in individuals with both low and very high BMI. In older hospitalized patients, the frailty prevalence varied from 27% to 80%. The prevalence of frailty in institutionalized older adults is less well defined, but varies from 29.2% to 68.8%.

The clinical relevance of frailty is mainly due to its being an important predictor of serious adverse outcomes, such as disability, health care utilization and death. The broader definition of frailty appears to be more precise than the Fried Scale in discriminating the risk of adverse outcomes, in particular mortality. A linear relationship between mortality rate and frailty as accumulation of deficits has also been demonstrated. In addition, physical frailty indicators are strong predictors of ADLs disability in community-dwelling older people. Slow gait speed and low physical activity/exercise seem to be the most powerful predictors followed by weight loss, lower extremity function, balance, muscle strength, and other indicators. Moreover, increasing frailty is associated with increasing length of hospital stay, nursing home institutionalization, and mortality in hospitalized patients. Consistently, a secondary data analysis in 1851 community-dwelling, Medicare fee-for-service enrollees, greater than or equal to

65 years old, who were discharged from the emergency department between January 2000 and September 2002, demonstrated that frailty was strongly associated with higher risk of hospitalization, nursing home admission, or death. As a consequence, there is consensus that frailty predicts high health care utilization and costs. Furthermore, frailty negatively impacts quality of life, directly or indirectly (through associated comorbidity). In addition, prescribing drugs for these vulnerable individuals is difficult and frequently complicated by iatrogenesis.

Finally, epidemiologic data on transition of frailty states according to Fried's definition show that nearly 60% of people over age 70 have at least one transition between any two of the three frailty states over 4.5 years. Transitions to states of greater frailty are more common than to states of lesser frailty, and the probability of transitioning from being frail to nonfrail is very low. Although a person who has already entered the frail state is unlikely to transition back to no frailty, the evidence that frailty is a dynamic process with older adults gradually progressing through different frailty states suggests the opportunity for prevention strategies.

COGNITION, DEMENTIA, AND FRAILTY

Traditionally, operationalization of frailty has been mostly focused on the physical aspects of the syndrome. However, the contribution of cognition to frailty has been increasingly recognized, and the complex relationship between frailty and cognitive functioning has been extensively explored. There is a higher prevalence of cognitive impairment and lower cognitive performance in frail older adults than in fit ones. Moreover, frailty increases the risk of future cognitive decline and incident dementia in longitudinal studies. As a consequence, the term "cognitive frailty" has been used to describe a clinical condition characterized by the simultaneous occurrence of both physical frailty and cognitive impairment, in the absence of a diagnosis of dementia or underlying neurologic conditions. In particular, the operational definition of cognitive frailty is based on the following criteria: (1) physical frailty; (2) mild cognitive impairment (MCI), according to the Clinical Dementia Rating (CDR, score equal to 0.5); and (3) exclusion of Alzheimer disease (AD) and other dementias. Moreover, it has been suggested that the occurrence of physical frailty should precede the onset of cognitive impairment, in order to differentiate between a physically driven cognitive decline versus a cognitive deterioration independent of physical conditions. However, despite the increasing interest in the complex relationship between physical deterioration and cognitive decline in older adults, no epidemiologic data on cognitive frailty have been produced yet. Therefore, future research in this field should better define the epidemiology and clinical presentation of this condition as well as the underlying biological and pathophysiologic pathways.

FRAILTY IN THE CONTEXT OF SPECIFIC MEDICAL CONDITIONS

The robust scientific progress generated in understanding functional status as a prognostic marker has induced other specialties to incorporate frailty into clinical decision making.

1. *Frailty to evaluate surgical risk.* Despite progress in medical and anesthesia support techniques, older surgical patients have an excess risk of postoperative adverse outcomes. The main reasons are the frequent presence of comorbid conditions and reduced functional reserve across multiple systems. In addition, surgical diseases and surgery itself are stressors that may alter physiologic homeostasis. Therefore, assessing frailty has a particular clinical relevance for older patients who are considered as candidates for surgery. Frail older adults who undergo surgery, in fact, are more likely than patients who are not frail to experience postoperative complications such as pneumonia, delirium, and urinary tract infections; have prolonged hospital stays; be discharged to nursing homes or long-term care facilities; and have higher mortality. Surgical decision making is very challenging due to the heterogeneity of health status and level of fitness among older adults and the paucity of appropriate assessment tools for predicting operative risks. Traditional risk assessment measures have substantial limitations as they are mostly based on specific comorbid conditions or on single organ system, and they do not estimate individual physiologic reserve. "Alternative" tools, whose cornerstone is the assessment of frailty, are emerging. One example is a multidimensional frailty score based on the following items: benign/malignant disease, comorbidity (Charlson index), albumin level, physical function (ADL and IADL), dementia (MMSE-KC), risk of delirium (Nu-NESC), nutrition (MNA), and mid arm circumference. This multidimensional frailty score was more useful than conventional methods for predicting outcomes in geriatric patients undergoing surgery.

2. *Frailty and cancer.* Emerging evidence suggests that the pathogenesis of age-related degenerative and cancer diseases may share cellular senescence as a common denominator. One of the major issues facing physicians who deal with older adults with cancer is the heterogeneity of their physiologic reserves and level of physical and cognitive fitness and, consequently, their ability to tolerate treatment and prognosis. Moreover, cancer and its treatments are often associated with comorbid conditions such as weight loss and cachexia, which may negatively affect patients' quality of life, tolerance to treatments, and ability to respond to rehabilitation. Polypharmacy, as result of the presence of comorbidity, is also an

important issue in older adults with cancer, and it is associated with high risk of adverse side effects and postoperative complications. Therefore, it is becoming part of oncologic practice to include comprehensive geriatric assessment (CGA) in the evaluation of older adults with cancer, with particular attention to functional status (ADL, IADL), presence of comorbidity, social support, cognitive status, and presence of geriatric syndromes. In geriatric oncology, in particular, CGA identifies reversible conditions that might interfere with the treatment of older patients, it ascertains an estimate of life expectancy and treatment tolerance, and it establishes a common language in the classification of older individuals as an alternative to the use of chronologic age. On the other hand, CGA is very time consuming; therefore, a number of screening tests have been proposed, such as the Vulnerable Elderly Survey 13 (VES-13). Patients who screen positive (ie, VES-13 score of 3 or higher) should undergo a complete CGA. In old and very old patients with a diagnosis of cancer, but who are apparently healthy, physically active, and cognitively intact, a different approach should be considered for estimating the status of individual physiologic reserves and susceptibility to stress. In these cases, the conceptual framework provided by the physical phenotype of frailty is particularly useful to estimate the risk of side effects of potentially harmful treatments and make the most appropriate choices among different treatment options.

3. *Frailty and chronic kidney disease (CKD).* Reduced renal function, even when still in the range considered "normal aging," is one of the main factors associated with unsuccessful aging. Older adults with the more severe stages of CKD are often frail individuals with reduced physiologic reserves, homeostatic dysregulation, comorbid conditions, polypharmacy, geriatric syndromes, disability, need for institutional care, frequent hospitalization, and high mortality rate. CKD even at earlier stages has been associated with clinical manifestations of frailty. The CHS showed that individuals with CKD have twofold risk of being frail and disabled because of disease-related conditions such as protein-energy wasting, anemia, inflammation, acidosis, and hormonal disturbances. Frailty is also extremely common among patients starting dialysis and is associated with adverse outcomes among incident dialysis patients, including higher risk of hospitalization and death. In these patients, frailty may be either a result of uremia or independent of CKD. Frail patients are started on dialysis earlier (at a higher estimated glomerular filtration rate) on average than nonfrail patients, although there are no data to suggest that frail patients derive any benefit from early initiation of dialysis either in the form of improved survival or functional status.

4. *Frailty and cardiovascular disease (CVD).* Frailty has become a high priority in the management of cardiovascular patients due to their increasing aging and complexity. Frailty is about three times more prevalent among persons compared with those without heart disease. In the CHS, frail subjects were more likely to have subclinical CVD, and subjects with subclinical CVD were more likely to have impaired physical or mental function during follow-up. Similarly, the Women's Health Initiative Study revealed that women with coronary artery disease (CAD) were more likely to develop de novo frailty over 6 years (12% vs 5%), and the Health, Aging, and Body Composition study showed that older adults with objectively measured frailty were more likely to develop CAD events (3.6% vs 2.8% per year). Frailty has been reported in 20% of patients aged greater than or equal to 65 years undergoing percutaneous coronary intervention (PCI) and in 27% of patients aged greater than or equal to 70 years with significant CAD at cardiac catheterization and is particularly common in patients undergoing TAVR. Frailty is also prevalent in patients with heart failure, which directly contributes to frailty by reducing exercise capacity and skeletal muscle function. Patients with CVD who are frail have a worse prognosis than nonfrail patients. For example, in one study of patients who underwent PCI, 3-year mortality was 28% for frail patients (using the Fried criteria) compared with 6% for nonfrail patients. Frailty is also a strong predictor of mortality in patients with chronic heart failure. In patients admitted to hospital with acute decompensated heart failure, simple measures of physical function have been associated with length of hospital stay, reduced activities of daily living, higher readmissions, and mortality. In one community-based study, the attributable risk associated with frailty in patients with heart failure was 35% for emergency department visits and 19% for hospitalizations. In patients referred for cardiac surgery, frailty has been associated with postoperative mortality and morbidity, and greater need for rehabilitation and institutional care following the procedure. In patients with severe symptomatic aortic stenosis treated by TAVR, frailty predicts need for institutional care and mortality 6 to 12 months after a successful procedure. Thus, identifying frailty has important implications for clinical care of older patients with CVD. The assessment of frailty is particularly relevant when counseling older patients with CVD regarding their prognosis following a procedure in order to plan personalized management and treatment, and increase their likelihood of positive outcomes.

5. *Frailty and diabetes.* In the CHS, 25% of frail subjects had diabetes, and 18% of prefrail subjects had diabetes, but only 12% of nonfrail subjects had diabetes. Furthermore, frail CHS participants were more likely to have higher glucose and insulin levels at baseline and on oral glucose tolerance testing than those who were not frail. Thus, there is no doubt that diabetes and frailty are closely interrelated, but what is uncertain is whether frailty leads to glucose disorders, glucose disorders lead to frailty, or that both are casually related to other common factors. Insulin resistance predicts incident frailty, and diabetes accelerates the loss of skeletal muscle strength—an important component of frailty. In old-old women from Women's Health and Aging Study II, an exaggerated and prolonged glucose and insulin response to an oral glucose tolerance test was observed in frail versus nonfrail or prefrail women, suggesting that dysregulation in response to glucose challenge may be a component of physiologic

vulnerability associated with frailty. On the other hand, the increased expression of inflammatory markers in frail older adults may negatively influence late-life glucose tolerance leading to the development of diabetes and may also have an adverse impact on the microvascular effects of diabetes itself.

6. *Frailty and HIV.* Patients with HIV experience accelerated aging and greater risk of geriatric syndromes such as frailty and difficulty with daily activities than HIV-negative people of the same age. Prevalence of frailty in younger HIV-infected individuals is similar to that in older adults, ranging from 5% to 20%. A decline in prevalence of frailty was observed with increased use of effective antiretroviral therapy. Duration of HIV infection, in addition to other markers of advanced HIV disease (CD4+ T-cell count < 350 cells/mm^3), are independently associated with the occurrence of a frailty-related phenotype. The presence of clinical AIDS, previous opportunistic illnesses, and CD4+ T-cell count less than 100 cells/mm^3 are further risk factors for HIV-related frailty. A low serum albumin, which may represent an end point of chronic low-grade inflammation from concomitant comorbidities, weight loss, and/or nutritional and metabolic disturbances, is also associated with HIV-related frailty and is an important independent predictor of death in untreated HIV-infected persons. Similarly to older adults, in HIV-infected persons frailty predicts a number of negative clinical and socioeconomic outcomes. For example, frail HIV-infected persons have greater comorbidity including chronic kidney disease, cognitive impairment, and depression. Furthermore, frail HIV-infected persons have higher rates of nonelective hospitalization and longer inpatient admissions.

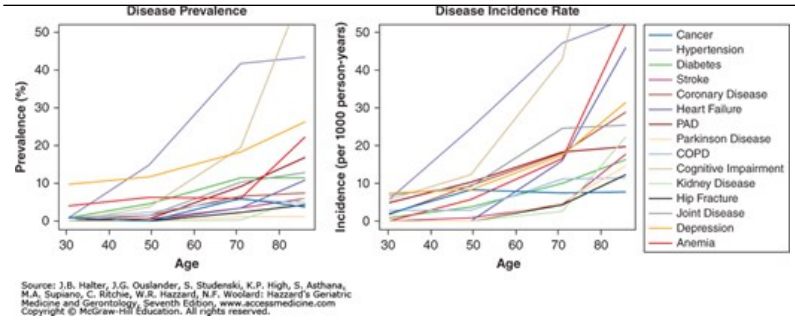
7. *Frailty and transplantation.* An increasing number of older adults are referred for and have access to organ transplantation and also are donating organs. Organ allocation systems vary by specific organ and by programmatic tendencies. For example, the lung allocation score, which includes age as a variable, grades disease severity and physiologic reserve. The model for end-stage liver disease (MELD) predicts waitlist mortality but predicts posttransplant outcomes only at scores above 35. Although short-term outcomes are acceptable for older transplant recipients across organs, long-term outcomes differ by age. Older donor organs also have been associated with inferior long-term outcomes, for example, increased risk for graft loss. Transplant recipients are often selected based on the likelihood of successful outcomes, and age is often used as a determinant. However, comprehensive risk assessment, based on stronger predictors than age and accounting for end points such as independence and quality of life, is needed to evaluate risk versus benefit for older recipients. One prospective study of 487 patients with end-stage liver disease referred for liver transplant demonstrated that frailty, defined using the Fried criteria, is a better indicator of quality of life than severity of liver disease measured as MELD.

MULTIMORBIDITY IS THE CLINICAL MANIFESTATION OF FRAILTY

As people age, they not only tend to lose their physical and cognitive integrity, but also become highly susceptible to several chronic diseases, such as congestive heart failure, chronic kidney disease, anemia, chronic obstructive pulmonary disease, and others. Both the prevalence and incidence of major chronic diseases increase with aging (**Figure 46-6**). Hence, if only by chance alone, the probability that a person would develop multiple chronic diseases increases with aging. Indeed, the term “multimorbidity”, namely the cooccurrence of at least two chronic diseases in the same person at the same time, is mainly used to refer to an age-related phenomenon. But chance is only part of the story. The multisystem dysregulation that occurs with aging causes morphologic and physiologic changes in multiple organs and physiologic processes. These changes result in progressive homeostatic perturbation, functional deterioration, and reduced reserves. When a certain threshold of dysfunction is reached, it becomes clinically manifest at a system level as a chronic disease. In other words, from a gerontologic perspective, multimorbidity is a milestone for multisystem age-related loss of resilience and increased vulnerability. Because the rate of biological aging between individuals is highly heterogeneous, the predisposition to multimorbidity is also heterogeneous. Therefore, in a population of individuals the severity of multimorbidity is higher than expected by chance. Consistent with this vision, biological aging is widely recognized as the main risk factor for most chronic diseases.

Figure 46-6.

Prevalence and incidence of major chronic diseases according to age group. InCHIANTI study, 1998–2014. COPD, chronic obstructive pulmonary disease; D, disease; F, fracture; I, impairment; PAD, peripheral artery disease. (From Ferrucci and Fabbri, unpublished data.)



Source: J.B. Halter, J.G. Ouslander, S. Studenski, K.P. High, S. Asthana, M.A. Supiano, C. Ritchie, W.R. Hazzard, N.F. Woolard: Hazzard's Geriatric Medicine and Gerontology, Seventh Edition, www.accessmedicine.com

Indeed, the relationship between multimorbidity and frailty has not been fully conceptualized yet. In most cases, despite a certain undiscussed overlap, the two concepts have been considered causally related, but distinct clinical entities, based on the epidemiologic observation that many but not all individuals with multimorbidity meet criteria for the frailty syndrome and vice versa.

If frailty is the aggregation of subclinical losses of reserve across multiple physiologic systems, and multimorbidity is the aggregation of multiple clinically manifested system failures, then frailty and multimorbidity can be viewed as diverse expressions (subclinical and clinical, respectively) of the increasing loss of resilience and homeostatic dysregulation which characterize aging itself. Attempts to operationalize frailty mainly focus on the identification of preclinical measures of high vulnerability to stressors with consequent increased risk to develop adverse outcomes, including disability and death. Similarly, the operationalization of multimorbidity provides a quantification of the clinical manifestations of such vulnerability.

Consistent with this idea, multimorbidity is strongly associated with the main clinical manifestations of frailty such as impaired physical function and cognitive decline. Accordingly, metrics of multimorbidity may be considered proxy measures of age-related multisystem dysfunction and accelerated aging. Indeed, multimorbidity is strongly associated with several aging phenotypes, including inflammation, changes in body composition, energetic impairment, and neurodegeneration (second layer of frailty—**Figure 46-2**). In the InCHIANTI study, higher baseline levels and steeper increases overtime of IL-6 strongly predicted accelerated longitudinal accumulation of chronic diseases in older adults. Moreover, multimorbidity was also related to higher resting metabolic rate (RMR) and RMR higher than expected for a certain age, sex, and body composition predicted future greater development of chronic diseases. In addition, obesity is associated with greater burden of diseases compared to normal weight and overweight status. However, in older adults who are obese at baseline, loss of weight over time rather than gain of weight is associated with the most dramatic rise in number of chronic conditions. In conclusion, weight loss, which is also one of the diagnostic criteria for the physical phenotype of frailty, when it occurs in obese older adults, may represent a sign of ongoing health status deterioration and steeper accumulation of multimorbidity.

The relationship between multimorbidity and the basic biological mechanisms of frailty is still largely unexplored. Age-related pathologies once thought to be distinct from each other are now understood to share the same underlying molecular and cellular mechanisms, some of which are also the biological underpinnings of the aging process. The idea that slowing aging and the biological processes leading to frailty can determine not only a gain in lifespan, but also importantly an increase in health span (the portion of life an individual spends in good health), has driven the birth of a new multidisciplinary branch of science, called geroscience.

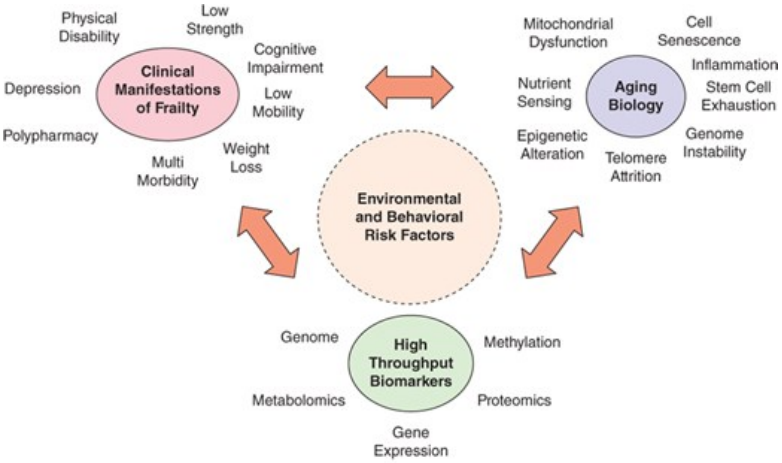
GEROSCIENCE AS A POSSIBLE INTERFACE BETWEEN FRAILTY AND PRECISION MEDICINE

The manifesto of geroscience, which embraces the conceptual approach outlined in the onion frailty model, is that health problems in older persons cannot be simply addressed by applying nosologic classification of diseases based on signs and symptoms and by the identification of a specific pathophysiology. Instead, understanding the biological mechanisms of aging would be considerably more informative about the causal nature of diseases, how and why disease manifestations and clinical course are modified by aging, and what treatments are likely to be more effective for prevention and cure of chronic diseases in the older people.

Biological mechanisms of aging are still poorly understood, but research in this area has made great progress over the last few decades (see Chapter 1). Research on the hypothetical mechanisms of aging is gaining momentum, and some of these hypothetical mechanisms of aging can now be tested in humans. Such testing offers the opportunity to verify whether one or more of these mechanisms are related and change in parallel with the major phenotypes of aging and frailty, thereby validating the hypothesis that they are true drivers of the aging process. While it would be difficult and prohibitively expensive to apply routinely sophisticated techniques of molecular biology to the evaluation of frail older patients, it may be possible to identify basic biomarkers that capture the biological nature of the processes at the core of frailty. These processes (illustrated in **Figure 46-7**) could be targeted for potential interventions.

Figure 46-7.

Operational definition of research aimed at understanding the relationship between accelerated aging and frailty. (From Ferrucci and Fabbri, unpublished data.)



High throughput genetic and genomic biomarkers are increasingly employed to study aging and age-related medical conditions and may have value in understanding the core of frailty and translate this knowledge into clinical applications. Studies that combine measures of aging biology, such as high throughput biomarkers and in-depth phenotyping, may create a convergence between geroscience and "precision medicine." Precision medicine assumes that individual patients can be classified into subpopulations that differ in some biological characteristics that make them susceptible to particular medical conditions or outcomes. Preventive or therapeutic interventions can then be tailored to those patients with specific characteristics, thereby maximizing effectiveness and sparing expense and side effects. Frailty appears to result from perturbing and stressful events that act on a background predisposition leading to multisystem dysregulation. The biological mechanisms responsible for the frailty syndrome could be identified as those that are cross-sectionally and longitudinally correlated with some predefined phenotypes. The nature of these relationships might be further described by a signature biomarker set derived from high throughput technology: genetic, gene expression, epigenetic, or proteomic biomarkers. Once these relationships have been robustly established, high throughput methods that are becoming progressively less and less expensive could be used to classify patients to receive different targeted therapeutic interventions.

The new paradigm of precision medicine provides an almost ideal entry for the frailty concept into the mainstream of modern medicine. Beyond the variety of operational definitions, at the heart of precision medicine is the attempt to better understand the pathology in the context of the physiology of a specific individual, so that prevention and treatment strategies can be selected that account for variability across individuals. To accomplish this goal, precision medicine relies on state-of-the-art molecular profiling, including but not limited to high throughput genetics, genomics, metabolomics, and proteomics and the emerging ability of computational biology and systems biology to extract meaningful information from "big data." An attractive feature of precision medicine is the agnostic approach to patient subgroup classification that excludes preconceived assumptions about etiology and pathophysiology. The biological mechanisms underpinning the aging process are not known, but research in model organisms suggests that one or a few biological processes are involved. Under the assumption that these processes are also involved in the pathophysiology of chronic diseases and frailty, namely that multimorbidity and frailty result from accelerated aging, the agnostic approach proposed by precision medicine may be able to capture their nature. Prevention and treatment strategies driven by precision medicine will have to take into account the core mechanisms of aging and, perhaps, will be able to distinguish pathologic conditions that have a unique, intrinsic pathophysiology and those that are mostly age related. To accomplish this goal, it is critical that the next-generation studies that derive the molecular signature of pathology include measures of multimorbidity and frailty, and that geriatricians and gerontologists be involved in the development of these new tools.

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