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REVIEW

Frailty and sarcopenia: definitions and outcome parameters

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Abstract An operational definition of musculoskeletal decline in older people is needed to allow development of interventions for prevention or treatment, as was developed for the treatment of osteoporosis. Frailty and sarcopenia are linked, but distinct, correlates of musculoskeletal aging that have many causes, including age-related changes in body composition, inflammation, and hormonal imbalance. With the emergence of a number of exciting candidate therapies to retard the loss of muscle mass with aging, the derivation of a consensual definition of sarcopenia and physical frailty

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becomes an urgent priority. Although several consensual definitions have been proposed, these require clinical validation. An operational definition, which might provide a threshold for treatment/trial inclusion, should incorporate a loss of muscle mass as well as evidence of a decrease in muscle strength and/or physical activity. Evidence is required for a link between improvements in the measures of muscle strength and/or physical activity and clinical outcomes to allow development of interventions to improve clinical outcomes in frail older patients.

Keywords Assessment · Frailty · Outcome · Pathophysiology · Sarcopenia · Treatment

Introduction

A healthy musculoskeletal system is vital for physical functioning. Over the years, the medical and pharmaceutical communities have focused more on the bones and joints than on the muscles. However, a decrease in skeletal muscle mass is a universal consequence of aging with a broad array of functional and metabolic consequences. Skeletal muscle has effects on a number of vital processes that are often not well appreciated [1]. Clearly, skeletal muscle is responsible for movement, and loss of muscle mass and quality results in weakness and reduced mobility. However, skeletal muscle has other critical functions. It is the largest reserve of protein in the body, and during periods of stress, undernutrition or starvation, it provides a continuous supply of amino acids to maintain protein synthetic rate in other vital tissues. Skeletal muscle is the primary site of glucose disposal, and diminished muscle mass may play a role in impaired glucose metabolism in patients with insulin resistance and type 2 diabetes. In addition, skeletal muscle is the major consumer of energy and contributor to basal metabolic rate (BMR) in the body, and loss of muscle is the primary cause of age-associated reduced BMR and decreased energy needs [2]. This age-associated loss of skeletal muscle mass, function, and quality is termed sarcopenia [3–6].

An operational definition of musculoskeletal decline in older people, incorporating specific and relevant outcome measures, is needed to allow development of interventions for prevention or treatment. Several groups have provided definitions of sarcopenia or physical frailty and suggested how these concepts may be assessed [6–12]. Baumgartner et al. defined sarcopenia as a deficiency in muscle mass [7]; the European Working Group on Sarcopenia in Older People (EWGSOP) define it as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes [6]; and the International Sarcopenia Consensus Conference Working Group (ISCCWG) as age-associated loss of skeletal mass and function [11] (Table 1). The EWGSOP provided an algorithm for screening and assessment (Fig. 1). Initial descriptions of sarcopenia as a loss of skeletal muscle mass with advancing age speculated that sarcopenia would predict a future outcome, such as risk of impaired mobility, fall, hospitalization, or mortality. Just as osteopenia predicts risk of osteoporotic fracture, it was thought that sarcopenia would be a powerful predictor of risk. Indeed, many have defined when an individual becomes "sarcopenic" using criteria previously used to define osteoporosis or two standard deviations lower than a young adult [7, 13, 14]. However, a growing consensus of scientists and practitioners is that sarcopenia should not be defined solely on the basis of muscle mass but also on aspect(s) of functional capacity [6].

Table 1 Comparison of sarcopenia definitions and assessments

	Baumgartner et al. [7]	EWGSOP [6]	ISCCWG [11]
Component measured	Muscle mass (ASM)	Muscle mass	Muscle mass
		Muscle strength, OR physical performance	Physical function
Method of measurement	DXA	DXA or BIA	DXA
		Grip strength Gait speed or SPPB	Gait speed
Cut-point	ASM/h^2 >2 SD below young healthy mean	>2 SD below young healthy mean	ALM/h^2 ≤7.23 (men) or ≤5.67 kg/m^2 (women) <1 m/s
Strengths	Simple	Measures both muscle mass and function	Measures both muscle mass and function
Weaknesses	DXA not widely available in all healthcare systems No measure of function		DXA not widely available in all healthcare systems

ASM appendicular skeletal muscle mass, *DXA* dual-energy X-ray absorptiometry, *SD* standard deviation, *BIA* bioimpedance analysis, *SPPB* short physical performance battery, *ALM* appendicular lean mass

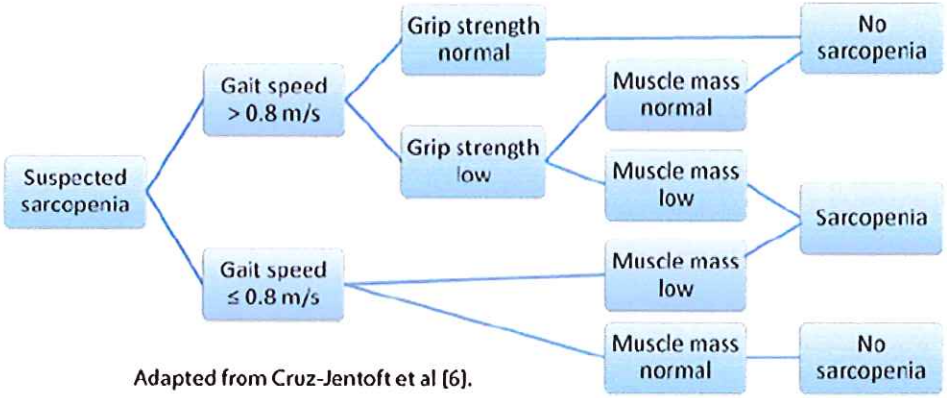

Fig. 1 Algorithm suggested by EWGSOP for sarcopenia case finding

The European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis set up a working group on sarcopenia and frailty because they saw a strong link between these conditions and the skeletal diseases that are the society's focus. In this paper, the authors assess current evidence, identify knowledge gaps, and seek to move towards consensus on conceptual and operational definitions of frailty and sarcopenia to allow development of treatments for these conditions. While it is well appreciated that sarcopenia is a universal feature of aging, the development of criteria for the diagnosis of sarcopenia is complex and must depend upon data linking muscle mass and functional capacity to morbidity and mortality outcomes common among geriatric patients.

Osteoporosis and sarcopenia

Osteoporosis is a skeletal disease that is associated with an imbalance between bone resorption and formation, which leads to a loss of bone mass and deterioration of bone microarchitecture [15, 16]. Recent research has shown that osteoclast activity is regulated by the RANK/RANK ligand pathway [17], while osteoblast activity is regulated through the Wnt signaling pathway [18]. Similarly, sarcopenia results from a disproportionate decrease in synthesis and/or increase in breakdown of skeletal muscle protein. Anabolic hormones and muscular activity drive this through the phosphatidyl inositol-3 system [19]. Muscle protein synthesis is stimulated through the activation of the mammalian target of rapamycin, which also inhibits atrophy by phosphorylating the protein FOXO. Glucocorticoids and myostatin inhibit the production of satellite cells, and inflammatory cytokines cause DNA fragmentation and apoptosis of these cells, resulting in increased skeletal muscle protein breakdown [11]. Other hormones and cytokines involved in the synthesis and breakdown of muscle include testosterone [20], insulin-like growth factor (IGF)-1 [21, 22], adrenal hormones [23], and insulin [24]. Several of these cellular interactions are similar to the control systems that link osteoblast and osteoclast function. However, the pathways involved in this process seem to be more complicated than those identified in osteoporosis. In addition, muscle provides a mechanical stimulus to bone tissue, and may also influence bone metabolism by secreting local growth factors (IGF-1, FGF-2) that can stimulate osteogenesis [25].

Although both slow and fast motor units are lost in age-related loss of muscle mass, loss of fast motor units is accelerated [26]. In addition, there appears to be fiber atrophy or loss of cross-sectional area of type II fast twitch fibers. As motor units are lost, the increased burden of work is transferred to the surviving motor units, which adapt through a net conversion of type II fibers to type I fibers. This results in an increase in the total percentage of muscle cross-sectional area occupied by type I fibers. This loss of fast motor units leads to the loss in muscle power necessary for actions such as rising from a chair, climbing steps, or regaining posture after perturbation of balance. Moreover, muscle tissue components are infiltrated by lipid, which is found within adipocytes as well as in the muscle fibers.

Definitions

Biological aging can be defined as deteriorative changes during post-maturational life associated with an increased risk of morbidity, functional decline, disability, and death [27]. There are many theories about why individuals age, which can be categorized as either genetic, random event, or alteration in genetic material. However, the process of deterioration is not determined solely by age, as non-diseased older individuals are heterogeneous in levels of impairment [28]. In addition, not all deterioration is directly linked to age, although there is some association between age-related changes in different systems [29].

Sarcopenia is, by its derivation, loss of muscle mass. However, several clinical definitions of sarcopenia in older people have been proposed (Table 1) [6–12].

Frailty is multi-system impairment associated with increased vulnerability to stressors and describes individuals

who are at increased risk of adverse health outcomes [30]. Frailty is inter-related, but not synonymous, with comorbidity and disability [31, 32]. Rockwood and Mitnitski [33] describe it as an accumulation of deficits (assessed as the Rockwood frailty index) and Fried et al. [31] as a medical syndrome (assessed as the Fried frailty phenotype). Both definitions have strengths and weaknesses (Table 2). The Fried physical frailty phenotype might capture sarcopenic older adults as the criteria are directly related to the development of sarcopenia. Individuals can be categorized as non-frail (0 Fried criteria present), pre-frail or intermediate (1–2 criteria) or frail (≥3 criteria) [31]. The Rockwood Index can be adapted in a similar manner to provide a proportionate expression of the number of deficits [33].

Frailty and sarcopenia are linked, but distinct, correlates of musculoskeletal aging (Table 3). Poor functional capacity, the hallmark of frailty, results from a large number of causes, not all of which are related to skeletal muscle amount or function. Frailty together with low muscle amount and/or poor muscle quality will provide a clinician a potential treatment goal.

While poor functional capacity in older people has multiple causes, a diagnosis of sarcopenia will be useful in establishing treatment guidelines that will be important for the development of new medicines specific for skeletal muscle. A single accepted definition and term is needed. Although ISCCWG and EWGSOP have defined sarcopenia and proposed specific diagnostic criteria, at the time of writing neither definition has been widely endorsed and nor have the diagnostic criteria been tested to determine predictive power for outcomes in older people.

Epidemiology

Sarcopenia is common in older people and its prevalence increases with age. In one study of community-dwelling older adults, for example, the prevalence of sarcopenia was ~10% in those aged 60–70 years and ~30% in those over the age of 80 years [34]. However, it is difficult to specify reliable values as a worldwide operational definition of sarcopenia applicable across racial/ethnic groups and populations lacks consensus, resulting in variation depending on the chosen definition and method of assessment (8–40% of people older than 60 years) [35]. The prevalence of frailty is even less well characterized. Sydall et al. [36] used the Fried criteria to estimate the UK prevalence of frailty in individuals aged 65–74 years at 8.5% in women and 4.1% in men.

Various measures of muscle function, including gait speed and grip strength, are predictive of mortality [37–39]. Gait speed is also a consistent risk factor for other adverse outcomes, including disability, cognitive impairment, institutionalization,

Table 2 Comparison of the Rockwood frailty index [23] and Fried frailty phenotype [21]

Rockwood frailty index			Fried frailty phenotype		
Theoretical basis and components	Advantages	Disadvantages	Theoretical basis and components	Advantages	Disadvantages
Accumulation of deficits	Tested in different populations	Highly variable components and numbers of components used	Medical syndrome	Easily operationalized	No clear rationale for criteria
Count of deficits: symptoms, signs, diseases, and disabilities	Permits evaluation in many systems	No distinction among functional impairment, comorbidity and disability	≥3 of unintentional weight loss, muscle weakness, exhaustion/fatigue, slowness, and less physically active	Validated as predictive of specific outcomes[a]	Variability in thresholds used
Sources of data on deficits[b]	Accommodates change Graded Conceptually simple Consistently associated with all-cause mortality	No indication of underlying mechanisms Operationalized as the 40-item FI-CGA Performance enhanced by weighting components		Dissociates comorbidity and disability	

[a] Incident falls, deficits in activities of daily living, hospitalization, mortality

[b] Clinical database, self-report, comprehensive geriatric assessment

Table 3 Discrete and overlapping components of the definition of frailty and sarcopenia

Frailty	Sarcopenia
Anemia	Muscle loss
Poor cognitive function	
Poor functional capacity	
Arthritis	
Poor balance	
Reduced cardiac function	
Obesity	

and falls [40]. Diminished muscle strength is significantly associated with higher blood glucose levels [41] and associated with reduced health-related quality of life [42] and longer hospital stay [43]. Muscle function and strength are, in turn, influenced by both muscle area and the amount of fat infiltration into muscle [44].

Environmental influences on muscle mass and function can act throughout adult life, as well as during development. Adult environmental factors include diet and exercise. Lower dietary protein intake is associated with skeletal muscle atrophy [45, 46] and an accelerated rate of bone loss [47]. Loss of muscle function can be mitigated by exercise and an active lifestyle that includes walking [48].

Developmental factors determine birth weight, and lower birth weight predicts weaker grip in older age [49, 50]. This suggests that sarcopenia may originate in utero and that developmental influences may have long-term effects on muscle function.

Although there is clear evidence linking impaired muscle function to poor health, there is little to show that improving measures such as hand grip or walking speed will lead to relevant improvements in clinical outcomes such as falls or hospitalization. Successful development of new therapeutic interventions will likely eventually demand demonstration of improvement in dependency and clinical outcomes of morbidity and mortality.

Pathophysiology

Sarcopenia and frailty have several causes [51]. The major factors include genetic heritability, nutritional status, physical activity, atherosclerosis, hormones, insulin resistance, and proinflammatory cytokines.

A growing body of literature demonstrates a striking effect of body fat on functional capacity in older people. The increasing prevalence of high amounts of body fat coupled with low skeletal muscle mass has been termed sarcopenic obesity [52], which is associated with a very high risk of impaired mobility in older people [44, 53–55].

Low-grade inflammation is seen in both sarcopenia and frailty. The theory of inflamm-aging suggests that the increase in inflammatory markers, particularly interleukin (IL)-6, seen with age leads to disease only in individuals with frailty genes or without genes associated with robustness [56].

This low-grade inflammation is a potential therapeutic target in sarcopenia, and exercise may be a treatment option in older people [57–62], although the response is attenuated by higher baseline levels of inflammation [63]. Adequate nutrition is required in addition to any exercise regimen.

Levels of anabolic hormones in men (testosterone [64–67], adrenal androgen [64], and growth hormone [68]) decline with age, and there is an interaction between the age-related decline in anabolic hormones in men and frailty (Table 4). In women, the age-related decrease in sex

Table 4 Hormones in sarcopenia and frailty

	Relationship	Physical sign
Men		
Hypoandrogenism [64]	Manifests as	↓ muscle strength
		↓ muscle mass
		↑ fat mass and altered distribution
↓ Testosterone [64]	Causes or accentuates	Frailty
↓ Testosterone [70, 71]	Predicts	frailty
↓ Testosterone [66]	Predicts	Risk of falls
↓ Testosterone [72, 73]	Predicts	mortality
↓ Estradiol [74]	Is associated with	↑ Risk of cardiovascular disease
↑ anabolic deficiency in chronic heart failure [75]	Is associated with	↓ Survival
Women		
↑ cortisol level with ↓ diurnal variation [76]	Is associated with	Frailty
≥ 2 of: ↓ IGF-1, ↓ DHEAS, ↓ free testosterone [77]	Is associated with	Frailty

IGF insulin-like growth factor, *DHEAS* dehydroepiandrosterone sulfate

hormones is clear, and there is also a decrease in dehydroepiandrosterone (sulfate), growth hormone and IGF-1 [69]. Abnormal hormone levels in women are also associated with frailty (Table 4).

Evidence is missing for the relationship between fat mass and muscle mass, as inflammatory cytokines are secreted by fat cells; the direction of any causal links between inflammation and frailty or alterations in the hormone profile and frailty. In addition, there are no relevant, well-defined, focused clinical endpoints for studies assessing hormonal therapy.

Assessment

Sarcopenia may be evaluated using the three measures defined by EWGSOP: loss of muscle mass in conjunction with decreased strength and/or physical performance (Table 5) [6, 30].

Various methods can be used to assess skeletal muscle mass. Dual energy x-ray absorptiometry (DXA), anthropometry and bioelectrical impedance analysis (BIA) are among the most commonly used, low cost and accessible methods, while magnetic resonance imaging (MRI), computerized tomography (CT) and creatinine excretion are the most specific methods; peripheral quantitative computed tomography, ultrasound and neutron activation have been used in some studies [70]. Each of these measurement methods has advantages and limitations (Table 6). DXA, BIA, MRI and CT provide indirect measurement of muscle mass.

None of these is ideal in routine clinical practice for reasons of cost, availability, or ease of use. DXA has been recommended for use in clinical practice [6], but access may be limited in many settings. As many of these methods are indirect, they rely on assumptions; in addition, changes in body water content will alter the accuracy of any such indirect measurements. The only direct measure of muscle mass currently available is 24-hour urinary creatinine excretion, which is impractical except in a research setting. A new direct measure of muscle mass—^{13}C-creatine dilution—is currently being evaluated for validity and ease of use, based on previous research demonstrating that ^{14}C-creatine dilution provides a valid measurement of muscle mass [71].

Strength can be measured using hand grip strength, which is correlated with most relevant outcomes of sarcopenia and frailty. However, grip strength may not provide an appropriate measure for assessment of the risk of impaired mobility.

Physical performance can be measured using a variety of tests: gait speed [39], the short physical performance battery (SPPB) [38], long corridor walk test [72], 6-minute walking test, timed get-up-and-go test, and stair climb test [6, 30, 73]. Gait speed is a quick, easy, and reliable measure, with a validated threshold of 1.0 m/s and meaningful clinical change of 0.1 m/s [74, 75]. Mortality is strongly associated with habitual gait speed [39]. The SPPB is more comprehensive, providing information on balance, gait, strength, and endurance from three simple physical tasks. It is very well characterized [38], and for every point difference in the SPPB score, there is a difference in mortality risk of 3–5 times [74, 75].

Pahor et al. suggest assessing muscle quality by means of a combined measure of DXA muscle mass and grip strength, as these methods are valid, reliable, specific to skeletal muscle, predictive of future health events, non-invasive, practical, low cost, and widely accessible [70].

The largest gap in knowledge about the areas of sarcopenia and frailty comes in the area of assessment. There is no proof of concept that improvement in any surrogate marker can predict a decreased risk of adverse outcomes (morbidity/mortality); no quantification of the value to patients of an increase in gait speed; no evidence of whether improvements in gait speed and SPPB improve outcomes; no accepted measure of or threshold for frailty; and no appropriate endpoints for trials of interventions to prevent or treat sarcopenia and frailty. In addition, there is no description of the clinical effect of a change from pre-sarcopenia to severe sarcopenia.

The way ahead

Aging is associated with a broad array of changes including loss of muscle and increased body fat. The final common pathway for these changes in body composition, increased prevalence of comorbid disease, inflammation, anemia, joint pain, and low levels of physical activity is a rapidly declining

Table 5 Proposed EWGSOP evaluations for sarcopenia [6]

	Proposed measurement	Pre-sarcopenia	Sarcopenia	Severe sarcopenia
Muscle mass	DEXA	Decreased	Decreased	Decreased
Strength and physical performance	Hand grip strength and Gait speed	Normal	Decrease in Strength or physical performance	Decrease in strength and physical performance

Table 6 Methods to assess muscle mass

		Anthropometry	BIA	CT	Creatinine excretion	DXA	MRI	Neutron activation	pQCT	Ultrasound
Advantages	Low cost	Y	Y			Y				Y
	Portable		Y						Y	
	Cross-sectional measurement of lean and fat mass areas in a specific part of the body			Y			Y		Y	
	Assessment of muscle quality			Y			Y		Y	
	Widely available					Y				
	Estimates of lean, fat, and bone tissues in the entire body or specific parts of it					Y				
Disadvantages	High cost						Y	Y		
	Limited accuracy	Y							Y	
	Affected by hydration status		Y							
	Exposure to radiation			Y		Y		Y	Y	
	Technically difficult to perform			Y			Y	Y		
	Diet restrictions the days before the urine collection				Y					
	No information about specific body districts (e.g., limbs)							Y		

Adapted from Pahor et al. [70]

functional capacity in older people that is characterized as frailty. Regulatory agencies are unlikely to approve any treatment aimed at the prevention of aging, which is a universal human phenomenon. Rather, strategies to increase muscle mass and improve function, as central features of both sarcopenia and frailty, should be a high priority. Opportunity lies in treating conditions that are common in older people and contribute to diminished functional capacity and loss of independence [76]. However, there are considerable challenges due to the complex nature of treating older frail patients with multiple chronic diseases and low functional reserve.

To develop effective treatments, it will be necessary to identify either a definition of sarcopenia with a threshold that provides a discrete population, or specific clinical disorders in sarcopenic populations (e.g., hip fracture, elderly with type 2 diabetes, aging HIV patients, elderly cancer survivors) that will benefit from such treatment, and in which these benefits can be demonstrated.

A Phase II proof-of-concept trial must show that any intervention increases both muscle mass and muscle function. The trial also needs to demonstrate that through its mechanism of action, the intervention stimulates muscle protein synthesis, reduces inflammation and cytokine levels, stimulates appetite and resolves nutritional deficiencies, and is durable.

A Phase III trial must demonstrate that the intervention improves functional capacity, increases muscle mass, and is safe over at least 1 year of treatment. The primary endpoint needs to be easily measured and any improvements need to provide clinically relevant change in outcomes. In such a trial, frailty criteria may provide a primary endpoint, for example, using measured gait speed, the SPPB, increased physical activity or decreased fatigue in the LCWT or 6-minute walk test. However, even if physical performance could be considered as a surrogate of disability, such that increasing levels of physical performance or muscle strength are associated with a risk-reduction of becoming dependent, the major and clinically relevant endpoint for Phase III trials remains the prevention of dependency. A real-life primary outcome, even if improvements in surrogates are achieved, should be based on dependency. The ongoing lifestyle interventions and independence for elders study (The LIFE study), a multicenter Phase III trial of physical activity or health education in 1,600 high-risk sedentary older persons, has operationalized the primary outcome of major mobility disability as the inability to perform the 400-meter walk [77, 78].

As yet, there are no discrete populations to target, and the disease-specific outcomes of interest to patients are not known. Furthermore, the effects of any treatment on frail older patients are not known, as they are rarely included in clinical trials.

Conclusion

Gaps remain in the definitions of sarcopenia and frailty and in our knowledge of the clinical effects of these conditions. Several consensual definitions have been proposed by different groups on both the conceptual and operational definitions of sarcopenia and frailty during the past decade but they still require clinical validation in large epidemiological studies. We suggest the term sarcopenic frailty, with a conceptual definition of the inability of active, autonomous, community-dwelling older people without current disabilities (but with low muscle mass) to cope with stressors, leading to increased risk of adverse health outcomes. This conceptual definition of sarcopenia was arrived at by consensus; however, at the present time, it has not been tested to determine predictive power for outcomes in older people. The development of validated operational consensus in this field could lead to a step change in both assessment of risk and development of novel therapies. In the case of osteoporosis, the original consensus definition made by the World Health Organization, using a threshold in the distribution of bone density at which osteoporosis could be designated (2.5 standard deviations below the young normal mean), and adopting a second threshold for low bone mass or osteopenia (between 1 and 2.5 standard deviations below the young normal mean) led to a marked increase in development of risk assessment strategies utilizing bone densitometry, as well as the innovation of several novel therapies including the oral and intravenous bisphosphonates, selective estrogen receptor modulators, strontium ranelate, and now biological therapies such as teriparatide and denosumab. The regulatory management of these agents all required a widely accepted definition of osteoporosis, as well as reference standards for measurement using bone densitometry. With the emergence of a number of exciting candidates to retard the loss of muscle mass with aging, the derivation of a consensual definition of sarcopenia and physical frailty becomes an urgent priority. The operational definition, which will provide a threshold for treatment/trial inclusion, of such a concept would then be a loss of muscle mass, as evidenced by a decrease in muscle strength and/or physical activity. The best approach to evaluating this decreased strength and/or physical activity would be to use the SPPB and disease-specific patient-reported outcomes.

Evidence is required for a link between improvements in measures of muscle strength and/or physical function and clinical outcomes to allow development of interventions to improve clinical outcomes in frail older patients.

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