REVIEW ARTICLE

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# Frailty in Older Adults

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CME

Frailty is a clinically identifiable state of diminished physiological reserve and increased vulnerability to a broad range of adverse health outcomes.[1-5] Frailty becomes more common as populations age. In a report covering 62 countries worldwide, the prevalence of frailty among community-dwelling persons ranged from 11% among those who were 50 to 59 years of age to 51% among those who were 90 years of age or older.[6] Older persons in acute care hospitals and nursing homes, those in low- or middle-income countries, and those with a socially vulnerable status are all at increased risk for frailty.[7]

In this review, we first provide a brief overview of frailty, including biologic mechanisms, measurement, and clinical management. This overview is followed by a discussion of approaches to individualizing clinical management on the basis of a patient's frailty level and interventions to reduce frailty and associated health outcomes. Finally, we note current evidence gaps and suggest future directions for managing frailty at scale in our aging society.

## Definitions of Frailty

Despite the existence of various definitions, two concepts of frailty predominate: frailty as a syndrome and frailty as a state of accumulated health deficits. With each version, frailty becomes more common with age and predicts adverse health outcomes.[1,2] The two concepts identify different subpopulations as frail. The Fried frailty phenotype[2,8] delineates a clinical syndrome resulting from altered metabolism coupled with abnormal stress responses. Characteristic features are exhaustion (first manifestation), weakness, slowness, physical inactivity, and weight loss (last manifestation).[9] The presence or absence and degree of frailty are determined by the number of features present: a person is considered to be "robust" if none of the features are present, "prefrail" if one or two are present, and "frail" if three to five are present. The presence of all five features indicates a critical transition, with the risk of death rising sharply and the chance of reversal diminishing.[10] The Fried frailty phenotype is distinct from the presence of multiple coexisting disorders and disability.[11]

The concept of frailty as deficit accumulation focuses on a state of poor health due to compounded age-related deficits.[1,12] The selection of deficits for evaluation depends on the context and available information (e.g., survey results, a comprehensive geriatric assessment, electronic medical records, administrative data, or biomarkers) and can include diagnoses, cognitive and physical impairment, disability, poor nutritional status, and laboratory abnormalities. The degree of frailty is quantified by means of a frailty index, which is the number of deficits present as a proportion of the total number of deficits assessed, with at least 30 assessed.[1] In most studies, less than 1% of participants have a frailty index greater than 0.70, a score suggesting a deficit burden that threatens survival.[1] Despite calls for a once-and-for-all consensus on the definition of frailty,[13] both the Fried frailty

KEY POINTS

**FRAILTY IN OLDER ADULTS**

- Assessing frailty enables clinicians to predict the outcomes and risks of health conditions, target the delivery of evidence-based interventions, and tailor clinical management, including decisions about stressful treatments.
- Frailty assessment should be used not as a convenient way to withhold potentially effective treatments but rather as a tool to facilitate patient-centered care.
- Management should be aimed at increasing physiological reserve in order to build robustness and resilience and prevent or mitigate stressors.
- The interventions that have proved to be efficacious in clinical trials (e.g., exercise, nutritional supplementation, and a comprehensive geriatric assessment) have not consistently shown similar effectiveness in routine care, which indicates implementation challenges.
- The benefit of routine frailty screening has been shown in high-risk clinical contexts (e.g., oncology and surgery); its benefit in primary care remains to be established.

phenotype and the deficit-accumulation approach remain in use.

## BIOLOGY OF FRAILTY

Our current understanding of the biologic mechanisms of frailty is evolving and incomplete.[1,2,14] It is thought that processes of accelerated aging at subcellular and cellular levels, including chronic inflammation, cellular senescence, mitochondrial dysfunction, and deregulated nutrient sensing,[15,16] give rise to dysfunction in multiple physiological systems and then to the clinical manifestations of frailty. The question of whether targeting these biologic processes can prevent or reverse frailty is an active area of investigation. Because most studies to date are preclinical, it remains uncertain how these findings may apply to humans.

Chronic inflammation, which may occur in response to noninfectious triggers such as cellular senescence and mitochondrial dysfunction, inhibits growth factor expression and increases catabolism, thereby contributing to sarcopenia and frailty.[17] Genetically altered mice that lack the antiinflammatory cytokine interleukin-10 have increased serum interleukin-6 levels, reduced oxygen consumption, and muscle weakness.[18] Triggered by DNA damage, cancerous mutations, and oxidative stress, some cells enter a state of permanent cell-cycle arrest (cellular senescence), during which they remain viable and secrete proinflammatory molecules (the senescence-associated secretory phenotype).[19] Senolytic agents, such as dasatinib and quercetin, remove senescent cells, leading to reduced inflammation and metabolic dysfunction in obese mice, improved lung compliance and reduced frailty in mice with idiopathic pulmonary fibrosis, and restoration of age-related bone loss in mice.[19] Chronic inflammation may also attenuate immune responses,[20] increasing susceptibility to infections and impairing the antibody response after vaccination.

Another key mechanism implicated in the development of frailty is mitochondrial dysfunction, caused by mutations in mitochondrial DNA, destabilization of respiratory chain complexes, and disruptions in mitochondrial homeostasis. The consequences are decreased production of cellular energy, increased production of reactive oxygen species, and inflammation.[14] In a study of superoxide dismutase 1 knockout mice, high levels of oxidative stress resulted in weight loss, muscle weakness, physical inactivity, and exhaustion, which were attenuated by dietary restriction.[21] In humans, mitochondrial dysfunction in skeletal muscle is associated with muscle weakness, exercise intolerance, and fatigue.[22] A reduced number of mitochondrial DNA copies, a marker of mitochondrial depletion, is correlated with the Fried frailty phenotype[23] and deficit-accumulation frailty.[24]

Deregulated nutrient sensing is also implicated in the development of frailty. Nutrient-sensing pathways involve mammalian target of rapamycin (mTOR) complex 1 (a nutrient sensor), as well as AMP-activated protein kinase (AMPK) and sirtuins 1 and 3 (nutrient scarcity sensors).[16] By activating AMPK and sirtuin pathways and inhibiting the mTOR pathway, caloric restriction offers health and longevity benefits.[25] In rhesus monkeys, long-term caloric restriction prevented the Fried frailty phenotype and ame-

liorated muscle weakness, slowness, physical inactivity, and exhaustion, as compared with ad libitum intake.[26] Inhibiting the mTOR pathway with rapamycin, activating AMPK with metformin, or activating sirtuins 1 and 3 with a nicotinamide adenine dinucleotide precursor improved muscle mass and function in animal models.[14]

Aging is associated with hormonal changes, such as a decline in anabolic hormones (e.g., dehydroepiandrosterone sulfate, testosterone, and growth hormone or insulin-like growth factor 1) and an increase in catabolic hormones (e.g., cortisol).[14] These hormonal changes inhibit the growth of skeletal muscle and promote its breakdown, possibly contributing to loss of resilience (the ability to recover from a stressor) and frailty.

## MEASUREMENT OF FRAILTY

Many instruments are available for measuring frailty, most of which predict adverse health outcomes. Brief screening tools abound for use in outpatient and inpatient settings, the emergency department, and preoperative clinics. These tools rely on patient report (e.g., the FRAIL [Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight] questionnaire[27]), clinical judgment (e.g., the Clinical Frailty Scale[28]), or electronic medical records.[29] Gait speed (<0.8 m per second) has 99% sensitivity for detecting the Fried frailty phenotype.[30] However, simple tools rarely provide sufficient information for mitigating risk through individualized care plans or tailored interventions. Multidomain tools based on a comprehensive geriatric assessment (e.g., the deficit-accumulation frailty index[1] and the Edmonton Frail Scale[31]) can reveal reversible conditions or target domains for interventions. A comprehensive geriatric assessment is a multidimensional evaluation performed by a multidisciplinary team or an expert clinician with the aim of determining an older person's medical, functional, physical, psychological, and socioenvironmental status in order to develop a coordinated and integrated plan for treatment and follow-up (more detailed information is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). For decision making about stressful treatments (e.g., chemotherapy or surgery), tools tested in specific treatment populations may be a better choice than general tools in predicting treatment outcomes. A guide for choosing a frailty assessment tool and electronic calculators for commonly used tools are available at eFrailty.org.

Performance measures (e.g., gait speed and handgrip strength) can be affected by acute conditions and may be impractical to use for hospitalized patients. Tools that do not involve performance testing can be useful in such patients. To avoid attributing symptoms of acute illness to frailty, the evaluation should include an inquiry about health status in the recent past (e.g., 2 weeks before the time of assessment). Knowledge of previous frailty status can reveal an older person's health trajectory and may form the basis for an annual review.[32] Worsening trajectories of the Fried frailty phenotype and deficit-accumulation frailty are associated with a higher risk of death[9,32] and a decline in quality of life.[33] Caution should be used in comparing results from different frailty tools. Modifying the assessment of the Fried frailty phenotype[34] or varying the list of deficits used in the frailty index,[35] which is common practice when measuring context-specific health states (e.g., the health of a patient being evaluated before undergoing surgery), can result in inconsistent assessments. To avoid misinterpretation, the frailty tool used should be specified. Guidelines are available to allow comparison of commonly used frailty tools.[36]

## FRAILTY SCREENING AND MANAGEMENT

The current evidence with respect to frailty screening and interventions is limited. Most of the clinical trials that have evaluated frailty interventions have been small, with heterogeneous trial populations and nonuniform screening tools, interventions, and outcome measures, all of which have contributed to low-quality evidence.[37-41] Despite these limitations, certain interventions have been shown to ameliorate frailty and associated outcomes (e.g., decreased mobility, muscle strength, and functional status and increased risk of falls). Although frailty assessment was used to determine eligibility in these trials, uncertainty remains regarding the effec-

tiveness of routine frailty screening as compared with usual care in improving outcomes and reducing health care utilization and costs. The usefulness of frailty screening has been most clearly shown in oncology[42,43] and surgery.[44,45] The interventions that have proved efficacious in the controlled environment of clinical trials have not consistently shown similar effectiveness in more pragmatic, routine care contexts.[46,47] But instead of concluding that these interventions lack efficacy, we need to put more effort into understanding how best to implement the interventions and make use of their benefits in routine care.

### APPROACH TO FRAILTY-GUIDED CLINICAL MANAGEMENT

The concept of frailty can be a useful tool in clinical practice, enabling clinicians to predict the outcomes and risks of age-related health conditions, target the delivery of evidence-based interventions, and tailor clinical management, including decisions about stressful treatments (e.g., chemotherapy and major surgery). Assessment of an older person's degree of frailty on a spectrum from fit to severely frail can provide a framework for applying evidence and principles of geriatric care (Fig. 1). The goal has two parts: first, to increase physiological reserve in order to build robustness (minimize damage from stressors) and resilience (repair damage), and second, to prevent or mitigate stressors. Care for persons without frailty should focus on increasing physiological reserve through a healthy lifestyle, management of chronic disease, and preventive care.

If frailty is suspected, a careful medical evaluation or comprehensive geriatric assessment should be performed to identify precipitants and exacerbating factors and to determine targets for interventions. Potentially high-yield clinical targets are depression, anemia, hypotension, hypothyroidism, vitamin $B_{12}$ deficiency, unstable medical conditions, and adverse drug events.[48] The aim of management is to preserve physiological reserve and prevent stressors in order to maximize functioning and quality of life, guided by the patient's goals and degree of frailty.

Frailty makes older persons more vulnerable to the risks associated with treatment. An important part of management is making routine care less hazardous for patients with frailty. The presence of frailty should not be used as a convenient reason to withhold potentially effective treatments but rather as an opportunity to facilitate patient-centered care. Aligning treatment with the patient's health priorities may reduce the burden of treatment and unwanted care.[49] Although it is necessary to minimize polypharmacy and avoid potentially inappropriate medications for patients who are frail, some treatments (e.g., exercise[50]) may be of great benefit to such patients. Incorporating frailty into a prognostic model improves the estimation of life expectancy, which in turn helps guide decisions about cancer screening.[51] Personalized, adaptive coping strategies, such as keeping daily routines in familiar surroundings, maintaining social connections, and mobilizing resources, can help patients perform self-care and uphold social roles, despite the limitations imposed by frailty.[52]

As frailty progresses, social support is important to ensure adherence to care plans and to assist with health management and daily activities. Heightened vulnerability makes vaccination and modification of the home environment important for preventing avoidable stressors.

Identifying persons with frailty who are nearing the end of life (end-stage frailty) can be challenging because of unpredictable patterns of functional decline. These persons often have all the features of the Fried frailty phenotype,[10] a deficit-accumulation frailty index approaching 0.70,[1] or complete dependence on help with personal care.[28] Management can focus on providing comfort and ensuring dignity through palliative care and hospice care.

### INTERVENTIONS FOR FRAILTY

Table 1 summarizes the evidence from meta-analyses and systematic reviews of randomized, controlled trials evaluating interventions to prevent or reduce frailty and associated outcomes in different patient populations. In general, interventions that affect a range of physiological systems (e.g., exercise and a comprehensive geriatric assessment) are efficacious in reducing frailty, whereas interventions that target a single physiological abnormality (e.g., hormone therapy) have not shown efficacy.

For community-dwelling older persons, exercise and oral nutritional supplementation, either

alone or combined,[37,38] and a comprehensive geriatric assessment[39] may have a positive effect on the Fried frailty phenotype. Exercise interventions, typically involving aerobic exercise and muscle strengthening at a frequency of one to four sessions per week for 30 to 60 minutes each,[38] as well as yoga[38,40] and tai chi,[38,41] are likely to enhance mobility and muscle strength, improve activities of daily living, and reduce falls. A comprehensive geriatric assessment may prevent unplanned hospitalization without affecting the risk of nursing home admission or death among

| | Fit | Prefrailty | Frailty | End-Stage Frailty |
|---|---|---|---|---|
| **Frailty Score** | Fried frailty phenotype, 0 points<br>Deficit-accumulation frailty index of <0.10<br>Score on Clinical Frailty Scale, 1–3 | Fried frailty phenotype, 1 or 2 points<br>Deficit-accumulation frailty index of 0.10 to <0.20<br>Score on Clinical Frailty Scale, 4 | Fried frailty phenotype, 3 or 4 points<br>Deficit-accumulation frailty index of 0.20 to <0.55<br>Score on Clinical Frailty Scale, 5–7 | Fried frailty phenotype, 5 points<br>Deficit-accumulation frailty index of ≥0.55<br>Score on Clinical Frailty Scale, 8 or 9 |
| **Goal** | Increase physiological reserve | Increase physiological reserve | Preserve physiological reserve and prevent avoidable stressors | Provide comfort |
| **Lifestyle** | Exercise and physical activity<br>High-quality diet<br>Social engagement | Exercise and physical activity<br>High-quality diet (protein intake)<br>Social engagement | Less intense exercise may be better tolerated<br>High-quality diet (protein intake)<br>Social engagement | Physical activity as tolerated<br>Diet as tolerated<br>Social engagement as tolerated |
| **Disease Management** | Apply disease-based guidelines | Apply disease-based guidelines | Consider trade-off between disease and treatment burden | Deescalate treatments |
| **Preventive Care** | Vaccination<br>Cancer screening | Vaccination<br>Cancer screening | Vaccination<br>Individualize cancer screening (time to benefit vs. remaining life expectancy) | Vaccination<br>Stop cancer screening |
| **Interventions for Frailty** | | Treat reversible causes of frailty<br>Exercise and physical activity<br>Nutritional counseling and supplementation<br>CGA and multidisciplinary intervention<br>Comprehensive medication review | Treat reversible causes of frailty<br>Rehabilitation (PT and OT)<br>Nutritional counseling and supplementation<br>CGA and multidisciplinary intervention<br>Comprehensive medication review | Comprehensive medication review |
| **Patient Engagement** | Patient-centered goal | Patient-centered goal | Patient-centered goal | Patient-centered goal |
| **Social Support** | Social support (family and caregiver) | Social support (family and caregiver) | Social support (family and caregiver) | Social support (family and caregiver) |

**Figure 1. Proposed Approach to Clinical Care of Older Patients According to the Degree of Frailty.**

Our proposed approach combines the evidence from randomized, controlled trials and best practices of geriatric care, both of which are necessary to provide evidence-based, person-centered care for older adults across the fit-to-frail spectrum. This approach should be used as a guide, as appropriate, on the basis of the clinical evaluation. For fit or prefrail persons, clinical management should focus on increasing physiological reserve and managing chronic conditions to prevent long-term negative health effects, including frailty and disability. For persons with frailty, management should focus on preserving physiological reserve and preventing or mitigating stressors. Because these persons have multiple disorders and polypharmacy, it is often necessary to realign treatment with the patient's personal goals and preferences. As a person approaches end-stage frailty (i.e., with all five features of the Fried frailty phenotype [exhaustion, weakness, slowness, physical inactivity, and weight loss, each representing 1 point], a frailty index [the number of deficits present as a proportion of the total number of deficits assessed] approaching 0.7, or complete dependence on assistance with personal care), management should focus on comfort and dignity. The cutoff points for the score on the Clinical Frailty Scale, which measures the risk of death or admission to an institution, are reasonable estimates and are not meant to be used as strict rules. When these cutoff points are first used in clinical practice or research, adjustment to the clinical context may be necessary. Management should be guided by patients' goals and preferences, and frailty should not be used to prevent access to potentially effective treatments. CGA denotes comprehensive geriatric assessment, OT occupational therapy, and PT physical therapy.

persons with frailty.[39,47] Medication optimization, which includes a comprehensive medication review and dose reduction or discontinuation of medications that have harmful effects or unclear benefits, may reduce the risk of death[63] and functional decline.[64] Supplementation with vitamin D,[56-58,62] n–3 fatty acids,[57-59] sex hormones,[69,70] or growth hormone[71] has little effect on frailty status, physical functioning, or activities of daily living.

For hospitalized older patients, exercise with oral nutritional supplementation may ameliorate the Fried frailty phenotype, reduce deficit-accumulation frailty, and improve mobility and activities of daily living.[53] Exercise alone or oral nutritional supplementation alone has equivocal benefits with respect to physical functioning and activities of daily living.[54,55] A comprehensive geriatric assessment reduces nursing home admission and hospital falls, prevents postoperative delirium and death, and improves mobility after hip fracture.[39] Medication optimization may reduce emergency department visits.[65]

For nursing home residents, medication optimization reduces the risk of falls, death, and hospitalization.[64,66] Exercise and yoga may improve mobility[38] and balance.[40] The benefit of oral nutritional supplementation and vitamin D supplementation is uncertain.[55,62]

### FRAILTY SCREENING IN PRIMARY CARE AND ACUTE CARE HOSPITAL SETTINGS

Given the availability of validated tools for frailty assessment and interventions that have been shown to be efficacious in randomized, controlled trials, a primary care–based integrative care model, encompassing routine frailty screening, a comprehensive geriatric assessment for patients with positive screening results, and tailored interventions, has potential for preventing and managing frailty. However, a meta-analysis of six randomized, controlled trials and two controlled studies conducted in the Netherlands showed that such a model failed to improve functional status, quality of life, and clinical outcomes at 1 year, as compared with usual care.[46]

A quality-improvement collaborative in England that focused on identifying patients with frailty and performing a comprehensive geriatric assessment within the first 72 hours after admission to an acute care hospital did not find reductions in the length of stay, in-hospital mortality, the 30-day readmission rate, or institutionalization during the 11-month period after the assessment.[72] These findings contrast with the positive effects of exercise,[38] oral nutritional supplementation,[37,53] and a comprehensive geriatric assessment[39,47] in clinical trials involving carefully selected patients. Possible explanations for the inconsistent findings include differences among the studies in the selection of participants, standard care in the comparison group, and fidelity of and adherence to the interventions. The effectiveness of an integrated care model in other health care environments warrants additional research.

### FRAILTY SCREENING BEFORE STRESSFUL TREATMENT

The rationale for frailty screening before stressful treatment is to improve candidate selection, proactively decrease risk, and offer person-centered care to improve treatment outcomes. In a cluster-randomized, controlled trial involving 40 oncology practices in the United States, the use of a summary of domain-specific impairments from a comprehensive geriatric assessment and tailored recommendations, as compared with usual care, reduced serious chemotherapeutic toxic effects without compromising treatment efficacy in older patients with cancer.[42] The percentage of patients who started less-intensive chemotherapy was higher in the comprehensive-geriatric-assessment group than in the usual-care group, which suggested that treatment intensity was modified on the basis of the comprehensive geriatric assessment.

In an Australian multicenter, randomized, controlled trial, a comprehensive geriatric assessment integrated into the care of older patients with cancer led to a better quality of life and fewer unplanned hospitalizations than usual care only.[43] In a large health care system in the United States, routine preoperative frailty screening followed by a discussion with surgeons about the patient's frailty status and prognosis, a palliative care consultation to clarify the patient's goals and expectations, and modification of the treatment plan (e.g., a decision to forgo surgery or to use a different procedure) was associated with a reduction in postoperative mortality.[44] Findings were similar in a study conducted after the National Health Service in England introduced a guideline

**Table 1. Evidence for Interventions to Prevent or Ameliorate Frailty and Associated Clinical Outcomes.***

| Intervention and Patient Population | Evidence (Quality of Evidence)† | Comments |
|---|---|---|
| **Exercise** | | |
| Community-dwelling older persons at risk for frailty | Exercise with nutritional intervention may ameliorate Fried frailty phenotype (low certainty)[37]<br>Exercise is likely to improve mobility (moderate certainty) and may ameliorate Fried frailty phenotype (low certainty), improve ADL (low certainty), and improve score on SOF scale‡ (very low certainty); effect on falls is uncertain (very low certainty)[38]<br>Yoga is likely to improve mobility and muscle strength (moderate certainty) and may improve balance (low certainty)[40] | Most of the evidence is for resistance training<br>The most effective exercise program is unknown; a typical program involved aerobic exercise and muscle strengthening, with 30–60 min/session and 1–4 sessions/wk[38]<br>Exercise in hospitalized older patients is typically supervised by a physical therapist, focusing on resistance training, with 20–90 min/session and 2–5 sessions/wk[53]<br>Exercise in hospitalized older patients did not increase falls[54] |
| Community-dwelling older persons with frailty | Exercise with nutritional intervention may ameliorate Fried frailty phenotype (low certainty) and improve mobility (very low certainty); effect on ADL is uncertain (very low certainty)[37]<br>Exercise is likely to improve mobility and ADL (moderate certainty) and may ameliorate Fried frailty phenotype (low certainty) and improve score on Edmonton Frail Scale (very low certainty)[38]<br>Tai chi may improve muscle strength (low certainty) and balance (very low certainty) and may reduce falls (low certainty); effect on mobility is uncertain (very low certainty)[41] | |
| Hospitalized older patients | Exercise with nutritional intervention may ameliorate Fried frailty phenotype (low certainty), decrease deficit-accumulation frailty (very low certainty), improve mobility (very low certainty), and improve ADL (very low certainty); effect on falls is uncertain (very low certainty)[53]<br>Exercise may not improve ADL (low certainty); effect on mobility is uncertain (very low certainty)[54] | |
| Nursing home residents | Exercise may improve mobility (very low certainty); effect on ADL and falls is uncertain (very low certainty)[38]<br>Yoga may improve balance (very low certainty); effect on mobility and muscle strength is uncertain (very low certainty)[40] | |
| **Nutrition** | | |
| Community-dwelling older persons at risk for frailty | Nutritional supplementation (ONS or fortified foods) may ameliorate Fried frailty phenotype (low certainty) and improve ADL (very low certainty); effect on mobility and risk of death is uncertain (very low certainty)[37,55]<br>Vitamin D supplementation does not improve mobility (high certainty) and may not improve muscle strength (low certainty) or deficit-accumulation frailty (very low certainty); effect on Fried frailty phenotype is uncertain (very low certainty)[56-58]<br>n–3 fatty acid supplementation may not improve mobility (low certainty), muscle strength (very low certainty), or deficit-accumulation frailty (very low certainty); effect on Fried frailty phenotype is uncertain (very low certainty)[57-59] | RDA for protein intake, 0.8 g/kg/day, may be inadequate in older persons because of anabolic resistance (the reduced ability to synthesize muscle protein in response to dietary protein and resistance exercise)<br>Experts recommend 1.0–1.2 g/kg/day for healthy older persons and 1.2–1.5 g/kg/day for patients with acute or chronic illness who are at risk for malnutrition, except for those with chronic kidney disease[60]<br>Protein ingestion in temporal proximity to resistance exercise may induce greater muscle protein synthesis[61] |
| Community-dwelling older persons with frailty | Nutritional supplementation (ONS or fortified foods) alone may ameliorate Fried frailty phenotype (low certainty) and improve mobility (very low certainty); effect on ADL is uncertain (very low certainty)[37]<br>Effect of vitamin D supplementation on muscle strength is uncertain (very low certainty)[62] | |
| Hospitalized older patients | Nutritional supplementation (ONS or fortified foods) alone may improve mobility (very low certainty); effect on muscle strength, ADL, risk of death, and hospitalization is uncertain (very low certainty)[55] | |
| Nursing home residents | Effect of nutritional supplementation (ONS or fortified foods) alone on muscle strength, ADL, risk of death, and hospitalization is uncertain (very low certainty)[55]<br>Effect of vitamin D supplementation on muscle strength is uncertain (very low certainty)[62] | |

| | | |
|---|---|---|
| **CGA and multidisciplinary intervention** | | |
| Community-dwelling older persons at risk for frailty | CGA and multidisciplinary intervention lower the risk of Fried frailty phenotype (high certainty) [39] | CGA is a systematic, multidimensional evaluation focused on determining a frail older person's medical, functional, physical, psychological, and socioenvironmental status in order to develop a coordinated, integrated plan for treatment and follow-up<br>For inpatients, CGA is performed by a specialist team or in a dedicated care unit |
| Community-dwelling older persons with frailty | CGA and multidisciplinary intervention ameliorate Fried frailty phenotype (high certainty) and may reduce unplanned hospitalization (low certainty) but do not reduce nursing home admission (high certainty) and are unlikely to reduce risk of death (moderate certainty); their effect on emergency department visits is uncertain (very low certainty)[39,47] | |
| Hospitalized older patients | CGA reduces nursing home admission (high certainty) and is likely to increase home discharge (moderate certainty)[39]<br>In patients with acute medical condition or injury, CGA reduces hospital falls (high certainty);[39]<br>In patients with trauma from hip fracture, CGA reduces delirium (high certainty), is likely to improve mobility (moderate certainty), may reduce risk of death (low certainty), and may improve ADL (very low certainty)[39]<br>In nonorthopedic surgical patients, CGA is likely to reduce delirium (moderate certainty)[39]<br>In patients undergoing emergency surgery, CGA is likely to reduce risk of death (moderate certainty)[39] | |
| **Medication optimization§** | | |
| Community-dwelling older persons at risk for frailty | Medication optimization may reduce risk of death (low certainty); it is unlikely to reduce hospitalization (moderate certainty) and may not reduce falls (low certainty)[63] | The American Geriatrics Society Beers criteria[67] and the STOPP and START criteria[68] can be helpful for medication optimization<br>Comprehensive medication review is often part of CGA |
| Community-dwelling older persons with frailty | Medication optimization may reduce functional decline (very low certainty); its effect on falls is uncertain (very low certainty)[64] | |
| Hospitalized older patients | Medication optimization may reduce emergency department visits (very low certainty) but may not reduce hospitalization (low certainty); its effect on ADL, falls, delirium, and risk of death is uncertain (very low certainty)[65] | |
| Nursing home residents | Medication optimization reduces falls (high certainty), risk of death (high certainty), and hospitalization (high certainty); it may improve score on Edmonton Frail Scale (very low certainty)[64,66] | |
| **Hormone supplementation** | | |
| Community-dwelling older persons at risk for frailty | Testosterone supplementation may reduce risk of death (low certainty) but may not improve mobility (low certainty); its effect on Fried frailty phenotype or deficit-accumulation frailty is uncertain (very low certainty)[69]<br>Effect of estrogen and progesterone replacement on mobility and muscle strength is uncertain in postmenopausal women (very low certainty)[70]<br>Effect of growth hormone supplementation on muscle strength is uncertain (very low certainty)[71] | |
| Community-dwelling older persons with frailty | Effect of testosterone supplementation on mobility is uncertain (very low certainty)[6] | |

* ADL denotes activities of daily living, CGA comprehensive geriatric assessment, ONS oral nutritional supplementation, RDA recommended daily allowance, START screening tool to alert to right treatment, and STOPP screening tool of older persons' prescriptions.
† Overall, high-quality evidence for frailty interventions is limited. The quality of evidence was evaluated on the basis of selected meta-analyses and randomized, controlled trials according to the GRADE (Grading of Recommendations Assessment, Development, and Evaluations) framework.
‡ The Study of Osteoporotic Fractures (SOF) scale includes three items: weight loss, the inability to rise from a chair five times without using arms, and reduced energy level, each representing 1 point.
§ Medication optimization includes comprehensive medication review and dose reduction or discontinuation of medications that have harmful effects or unclear benefits.

that provided a financial incentive for hospitals to include an assessment by a geriatrician for all older patients admitted with a serious injury.[45]

"Prehabilitation" programs, aimed at minimizing modifiable risk factors for poor surgical outcomes by typically focusing on exercise, nutritional counseling and supplementation, techniques to reduce anxiety, and smoking cessation for 4 weeks before surgery, may facilitate functional recovery after orthopedic surgery[73] and colorectal cancer surgery.[74] ("Prehabilitation" refers to a proactive approach to enhance a patient's physical and mental health before a stressful treatment.) The effectiveness of these programs in patients with frailty or in those undergoing other types of surgery remains uncertain.

## EVIDENCE GAPS AND FUTURE DIRECTIONS

Some interventions are beneficial for persons who live with frailty, yet the benefit of routine frailty screening, followed by tailored interventions, has not been consistently shown outside selected clinical settings (e.g., oncology and surgery). This discrepancy calls for additional research on strategies for identifying frailty (routine vs. targeted screening), the choice of screening tools, and the approach to intervention in routine care. Evidence is lacking regarding interventions to prevent or reverse frailty and their cost-effectiveness, the use of standard sets of outcome measures for evaluating frailty interventions, and the evaluation of treatment effects according to the degree of frailty.[5]

Unmet needs exist across the spectrum of care, but given the high stakes and immediacy of consequences, making hospital care safer for older adults with frailty should be seen as a high priority. Geriatric cardiology, geriatric oncology, orthogeriatrics, and related specialties may prove to be workable models for other fields, as long as such approaches are taken as a testable hypothesis and not as a fait accompli. Geriatrics uses complex interventions, resulting in individualized care plans for persons with complex needs. Such approaches merit emulation. In some countries (e.g., France, Canada, and China), community-based screening and management have been initiated. The long-term effectiveness of this effort has yet to be determined. A better understanding of the biology of frailty will aid in the identification of modifiable risk factors[4] and the development of potential therapeutics (e.g., "geroprotectors"[19]) for the prevention and treatment of frailty.

Given the pressing need for evidence, the heterogeneity of health care systems, and the costly and time-consuming nature of randomized, controlled trials, such trials are often impractical. One innovative strategy to address this challenge is the hybrid effectiveness–implementation study.[75] This study design not only evaluates the effectiveness of an intervention in real-world, local contexts but also explores the best ways to implement it. For decision makers, the advantage lies in the rapid uptake of these interventions, with consideration of local factors that affect implementation at specific sites. In the absence of compelling evidence favoring one frailty tool over another, such studies can guide decision makers in selecting the most appropriate measure. Another strategy is knowledge translation, in which research evidence is assembled and implemented. This process involves adapting, evaluating, and advancing the evidence in various clinical settings. An example of knowledge translation is the adoption of orthogeriatric care across trauma centers in England.[45]

## CONCLUSIONS

Assessing frailty enables clinicians to understand the variability in health status among older adults, provide care tailored to the individual patient's goals and health needs, and make decisions about stressful treatments on the basis of the patient's vulnerability. Frailty-guided clinical care has the potential to overcome the ineffectiveness of current models of care by treating older persons holistically rather than treating a fragmented collection of illnesses. To fully realize the benefits of frailty-guided clinical care, additional research is needed to narrow the gaps in our knowledge of measurement, new treatments, clinical management, and training for clinicians across diverse settings.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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