Review Article

Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care

Linda P. Fried,[1,2,3] Luigi Ferrucci,[3] Jonathan Darer,[4] Jeff D. Williamson,[5] and Gerard Anderson[2]

Departments of [1]Medicine, [2]Epidemiology, and [3]Health Policy and Management, The Johns Hopkins
University School of Medicine and Bloomberg School of Public Health, Baltimore, Maryland.
[4]Longitudinal Studies Section, Clinical Research Branch, National Institute on Aging, Bethesda, Maryland.
[5]Mid-Atlantic Permanente Medical Group, Baltimore, Maryland.
[6]Wake Forest University School of Medicine, Winston-Salem, North Carolina.

Three terms are commonly used interchangeably to identify vulnerable older adults: comorbidity, or multiple chronic conditions, frailty, and disability. However, in geriatric medicine, there is a growing consensus that these are distinct clinical entities that are causally related. Each, individually, occurs frequently and has high import clinically. This article provides a narrative review of current understanding of the definitions and distinguishing characteristics of each of these conditions, including their clinical relevance and distinct prevention and therapeutic issues, and how they are related. Review of the current state of published knowledge is supplemented by targeted analyses in selected areas where no current published data exists. Overall, the goal of this article is to provide a basis for distinguishing between these three important clinical conditions in older adults and showing how use of separate, distinct definitions of each can improve our understanding of the problems affecting older patients and lead to development of improved strategies for diagnosis, care, research, and medical education in this area.

I N 1990, an American Medical Association white paper concluded that "one of the most important tasks that the medical community faces today is to prepare for the problems in caring for the elderly in the 1990s and the early 21st century" (1). This report particularly emphasized the growing population of *frail*, vulnerable older adults, "the group of patients that presents the most complex and challenging problems to the physician and all health care professionals." The vulnerable subset of the older population has also been identified as those older adults with *multiple chronic conditions, or comorbidity* (2,3), or those who are *disabled or dependent* (4). In fact, these three terms, frailty, comorbidity, and disability, are often used interchangeably to identify the physically vulnerable subset of older adults requiring enhanced care. However, recent research supports geriatricians' perceptions that these are distinct clinical entities, although interrelated, and that clinical management of each of these has its own unique content and challenges. If this is the case, we would gain from defining how these concepts are distinct.

We posit that improved clarity as to definition and criteria for distinguishing these three conditions could improve diagnostic accuracy and development of effective, targeted strategies for prevention and treatment. To support this goal, this article offers, first, definitions for each of the three concepts based on current knowledge and supporting evidence, so as to distinguish them, and considers the challenges at present in establishing definitive criteria. Second, we

describe the interrelationships of frailty, comorbidity, and disability. Third, we describe clinical presentations of these conditions and discuss the issues in clinical management for older adults who have each one, or two, or three of these conditions. Finally, we consider the future research questions that must be answered to further the applicability of these concepts to improving clinical practice and to facilitating clinical research.

MAJOR COMPONENTS OF HEALTH STATUS IN AN AGING POPULATION: THREE DISTINCT CONCEPTS

Disability

Disability is defined as difficulty or dependency in carrying out activities essential to independent living, including essential roles, tasks needed for self-care and living independently in a home, and desired activities important to one's quality of life (4,5). While disability is, in some contexts, defined as a social phenomenon (6), i.e., one's ability to carry out one's roles in life, it is also a medical entity. Physical disability is mostly diagnosed by self-report of difficulty in specific tasks, but objective, performance-based tests of function also exist. It is recommended by several organizations that clinicians screen for disability in self-care tasks (Activities of Daily Living, ADL) and tasks of household management (Instrumental Activities of Daily Living, IADL) on an annual basis in persons aged older than 70 years (7–9). In addition, new

Table 1. Characteristics of Moderately and Severely Disabled Women, Aged 65 to 101 Years, in the Community: The Women's Health and Aging Study I ($n = 1002$)

Characteristic	
Chronic diseases	
Mean no.	4.3
Range	1–13
Frail	28%
Disability (difficulty in task)	
Walking 2–3 blocks	74%
Meal preparation	19%
Using telephone	10%
Bathing	45%
Dressing	21%
Homebound	15%
Live alone	46%
Still drive	25%
Sensory impairment	
Trouble with blurred vision	37%
Not able to see well enough to	
recognize someone across the room	5%
Difficulty with hearing hampers	
personal or social life	9%

screening methods can be used to identify older adults at high risk of mobility difficulty (10).

Physical disability occurs frequently in older adults. An estimated 20%–30% of community-dwelling adults aged older than 70 years report disability in mobility, IADLs (tasks essential to household management, such as meal preparation, shopping, and managing money) and/or ADLs (basic self-care tasks, such as bathing, dressing, and eating); the frequency of disability rises steadily with age among those aged 65 years and older (5). To provide an example of the import of such disability in peoples' lives, Table 1 shows the frequency of difficulty with household and self-care tasks in the one third most disabled older women living in the community. Although perception of ''difficulty'' is the most frequently used definition of disability, in some instances disability is defined as the need for help from another person in performing essential tasks. This is particularly important for the most disabled, dependent subset of older adults, who reside in nursing homes: approximately 5% of those aged 65 years and older.

Physical disability in late life is, in the main, an outcome of diseases and physiologic alterations with aging, with the impact of these underlying causes modified by social, economic, and behavioral factors as well as access to medical care. Individual diseases, specific pairs of comorbid diseases, comorbid impairments (such as muscle weakness and balance decrements or decreased exercise tolerance), and frailty itself (see below) are identified risk factors for physical disability (11,12); these may act independently or, more often, in synergistic combinations. Approximately half of disability in older adults develops chronically and progressively in association with underlying severity of disease, comorbidity, and frailty; the other half develops acutely, or catastrophically, in association with acute clinical events such as hip fracture or stroke (13). While disability

itself is an adverse health outcome, it is also a risk factor for other adverse events. Mobility disability predicts subsequent difficulty in IADLs and ADLs (14,15), and difficulty in these tasks is predictive of future dependency (16). Further, disability (defined as difficulty in these tasks), independent of its causes, is associated with an increased risk for mortality (17), hospitalization and high health care costs (see Table 2), need for long-term care (11,12), and higher health care expenditures (18).

Frailty

It is generally agreed that frailty is a state of high vulnerability for adverse health outcomes, including disability, dependency, falls, need for long-term care, and mortality. The challenges in finding a standard definition of frailty that could be widely recognized and valid in different settings makes any estimation of prevalence approximate and tentative. However, the American Medical Association has stated that as many as 40% of adults aged 80 years and older are frail (1). It is also thought that the vast majority of the 1.6 million elderly nursing home residents in the United States are frail (19). Thus, frailty occurs in a significant subset of older adults; if correct, this offers some evidence of its import. Because of the similarity with disability in associated outcomes (with the exception of frailty itself being a cause of disability), and the frequency of co-occurrence of frailty and disability (see below), there has been much definitional confusion between frailty and disability/dependency. However, there is increasing consensus that differentiating frailty from disability may improve our understanding of the aging process and offer new opportunities for prevention and care in clinical geriatrics. According to current views, frailty can be defined as a physiologic state of increased vulnerability to stressors that results from decreased physiologic reserves, and even dysregulation, of multiple physiologic systems. This decreased reserve results in difficulty maintaining homeostasis in the face of perturbations (20–24), whether they are extremes of environmental temperature, exacerbations of a chronic disease, an acute illness, or an injury. There are numerous systems in which such physiologic decrements in mass or function have been demonstrated with age, including neuromuscular, such as sarcopenia and decrease in muscle fiber function; osteopenia; dysregulation of the hypothalamic axis, of inflammation and of immune function; and even heart rate variability (21,24). Frailty is an *aggregate* expression of risk resulting from age- or disease-associated physiologic accumulation of subthreshold decrements affecting multiple physiologic systems. Although the early stages of this process may be clinically silent, when the losses of reserve reach an *aggregate* threshold that leads to serious vulnerability, the syndrome may become detectable by looking at clinical, functional, behavioral, and biological markers.

Central to the clinical definition of frailty has been the concept that no single altered system defines this state, but that multiple systems must be involved. The hypothesized subclinical dysregulations of frailty, as above, are under active investigation (24,25–32). However, it appears that these multisystem dysregulations become clinically apparent

Table 2. Utilization Patterns for Adults Aged 65 Years and Older With Comorbidity, With or Without Disability

Number of Chronic Conditions	Disability and/or Functional Limitation*	Total Inpatient and Medication Costs	Percent Hospitalized	Mean Number of Physician Visits	Mean Number of Home Care Visits	Mean Number of Prescription Drugs
None	No	$316	4%	2.1	0.1	2.7
None	Yes	$790	8%	3.0	4.5	6.4
2 or more	No	$2141	15%	8.0	1.2	19.4
2 or more	Yes	$4865	28%	10.2	27.7	23.5

Notes: *Disability and/or functional limitation defined in Medicare Expenditure Panel Survey as physical or mental impairments with or without substantial limitation or disability in 1 or more major life activities. Specifically, this included any of the following: 1) need for help or supervision with any activities of daily living or instrumental activities of daily living; 2) use of assistive technology; 3) difficulty walking, climbing stairs, grasping objects, reaching overhead, lifting, bending or standing for long periods of time; 4) any limitation in work, housework or school; 5) social/recreational limitations; 6) cognitive limitations such as confusion or memory loss, problems making decisions, or requiring supervision for their own safety; 7) deafness or difficulty hearing (5).
    From 1996 Medicare Expenditure Panel Survey.

either when unmasked by stressors or in a clinical phenotype of a final common pathway (21,22). Clinical consensus as to that phenotype has been reported by numerous authors to include wasting (both loss of muscle mass and strength, and weight loss), loss of endurance, decreased balance and mobility, slowed performance and relative inactivity, and, potentially, decreases in cognitive function (21,34).

These clinical observations were systematically assessed (by L.F. and J.D.W.) in a survey of geriatricians at six academic medical centers at Wake Forest University, Mt. Sinai School of Medicine, University of Tennessee, Saint Louis University, Johns Hopkins University, and Oxford University (Britain). A standardized, self-administered questionnaire was distributed by one local member to all geriatricians in their program, and then returned by mail to the developers of the survey (L.F. and J.D.W.). There was 100% response by 62 geriatricians. In this survey, we first asked the respondents whether frailty and disability were the same (21). As shown in Table 3, 98% of responding geriatricians stated that frailty and disability are separate clinical entities; rather, they thought them causally related. Among these same geriatricians, 97% supported a statement that frailty involves the concurrent presence of more than one characteristic. At least 50% cited each of the following characteristics as likely to be observed in association with frailty (in descending order): undernutrition, functional dependence, prolonged bed rest, pressure sores, gait disorders, generalized weakness, aged >90 years, weight loss, anorexia, fear of falling, dementia, hip fracture, delirium, confusion, going outdoors infrequently, and polypharmacy.

To explore thresholds for clinical identification of a patient as frail, these geriatricians were presented with standardized case scenarios developed for this purpose (by L.F. and J.D.W.). In these, they were asked to rank a series of clinical profiles as to the likelihood of frailty, scored on a scale from 0 (not frail) to 100 (frail). The results are presented in Table 4 for several representative profiles, displaying the aggregate mean scores from the respondents. The results support the impression that clinicians identify "frailty" in the presence of a critical mass of consequences of disease and aging-related changes, including: a) generalized weakness, b) poor endurance, c) weight loss and/or undernourished, d) low activity (even homebound), and e) fear of falling and/or unsteady gait. Individual diseases were not sufficient for identification of those who were frail, nor were any two

disease(s), or disability alone. In the presence of disease, other manifestations—which may or may not be a result of the disease—must also be present to constitute frailty clinically. Cognitive compromise may also be a component of frailty in some persons, although its role is less well defined. In sum, geriatricians' perceptions suggest that a critical mass of impairments or geriatric conditions add up to the phenotype of frailty, more than any one condition or disease.

All of the above findings indicate that frailty is a distinct entity recognized by clinicians, with multiple possible manifestations and no single manifestation, by itself, being sufficient or essential in the presentation. This definition is consistent with that of a medical syndrome (35). Building on the clinical consensus and research evidence to date, a phenotype of the clinically frail older adult was recently operationalized, based on the presence of a critical mass of three or more core "frail" elements, with the core entities being weakness, poor endurance, weight loss, low physical activity, and slow gait speed (21,23). This definition was tested in the Cardiovascular Health Study, a sample of 4317 community-dwelling adults aged 65 years and older who lived in four communities in the United States (23). Seven percent of community-dwelling adults aged over 65 years in this population were frail; the proportion increased steadily with age, up to 30% of those aged 80 years and older. To offer criterion validity for this definition, it was demonstrated that the presence of frailty significantly predicted disability and other adverse outcomes in older adults. This is shown in Table 5: Frailty predicted 3-year incidence or progression of disability in both mobility and ADLs, independent of comorbid diseases, health habits, and psychosocial characteristics (23). These findings provided evidence that frailty, as defined, is a separate entity and an independent cause of physical disability.

Table 3. Geriatricians' Position on the Relationship Between Frailty and Disability ($N = 62$)

Question	No (%)	Response Yes (%) Sometimes	Usually/Always
Are frailty and disability the same?	97.5	2.5	—
Is disability a cause of frailty?	12.5	75.0	12.5
Is frailty a cause of disability?	10.0	50.0	40.0

Table 4. Geriatricians' Ranking of the Likelihood of Frailty* for Specific Clinical Profiles: Survey of Geriatricians at 6 Medical Schools (U.S. and Britain, N = 62)

Clinical Profile	Frailty Score (Mean ± SD)*
A. 1. Arthritis; independent in ADLs and IADLs	13.6 ± 20
2. 1. plus depression	25.3 ± 17
3. 1. plus anxiety about gait stability/security (no falls)	28.3 ± 19
4. 1. plus poor stamina, goes outdoors infrequently	45.9 ± 23
5. 3. plus history of 2 falls in past 4 months	52.3 ± 23
B. 1. Systolic Hypertension	5.8 ± 13
2. 1. plus arthritis	12.6 ± 14
3. 2. plus diabetes, well controlled on oral agents	15.3 ± 16
4. 3. plus fatigues on performance of ADLs	30.1 ± 20
5. 4. plus mild dementia (MMSE = 25)	40.1 ± 23
6. 5. plus gait unsteady; in bed or chair most days	64.6 ± 24
C. 1. Dementia (MMSE = 20); dependent in IADLs; independent in ADLs	30.2 ± 22
2. 1. plus generalized weakness; goes outdoors infrequently	48.3 ± 22
3. 2. plus unintended weight loss of 20 lbs.	74.3 ± 20
D. 1. Excessive fatigue with:	
a. heavy housework (e.g., vacuuming)	18.5 ± 18
b. walking around the block	22.3 ± 20
c. climbing 2 flights of stairs	22.4 ± 19
d. light housework (e.g., dusting)	27.8 ± 19
e. making a bed	31.6 ± 20
f. walking around the house	31.8 ± 21
2. Steadies self with furniture or shopping cart when walking around home or shopping	36.6 ± 23
E. 1. Unintended weight loss (20 lbs)	30.3 ± 22
2. 1. plus fear of falling	42.6 ± 22
3. 1. plus weakness and secondary difficulty with ADLs	66.1 ± 21
F. 1. Osteoporosis; history of single compression fracture	21.3 ± 20
2. 1. plus generalized weakness	37.3 ± 23
3. 2. plus has fallen 2 times in past 3 months	60.2 ± 23
4. 3. plus unintended 20 lb weight loss	79.1 ± 23
G. 1. Anxiety about gait stability and security; fear of falling; goes outdoors infrequently (once a week); appetite good	40.4 ± 23
2. 1. plus poor appetite, 20 lb weight loss	63.6 ± 24
H. 1. Occasional urinary incontinence	5.8 ± 13
2. 1. plus unsteady gait	32.5 ± 20
3. 1. plus undernourished	45.9 ± 23
4. 3. plus difficulty with ADLs due to weakness	76.0 ± 18

Notes: *Frailty score = mean of all scores assigned by 62 geriatricians for probability of frailty in a given case scenario, with probability range from 0 (not frail) to 100% (frail).

SD = standard deviation; ADL = activities of daily living; IADL = instrumental activities of daily living; MMSE = Mini-Mental State Exam.

Comorbidity

At first blush, comorbidity should be the most straightforward concept to define medically, compared with disability and frailty. Its formal definition is the concurrent presence of two or more medically diagnosed diseases in the same individual, with the diagnosis of each contributing disease based on established, widely recognized criteria. In this sense, the concept of comorbidity could be viewed as an interface between the geriatric paradigm of health and the more traditional medical definition of disease. With aging, the presence of comorbidity increases markedly, in large part because the frequency of individual chronic conditions rises with age. For example, after age 65, 48% of community-dwelling persons in the United States report arthritis, 36% hypertension, 27% heart disease, 10% diabetes, and 6% a history of stroke (2,5). As a result of these prevalences, 35.3% of the population in the United States at ages 65–79 reports two or more diseases, and this reaches 70.2% at age 80 years and older (36). Analysis of Medicare claims data shows that two thirds of all beneficiaries aged older than 65 years have two or more chronic conditions, and one third have four or more (37). Comorbidity is associated with high health care utilization and expenditures (Table 2), with 96% of annual Medicare spending attributable to beneficiaries with multiple chronic conditions (37). Additionally, comorbidity heightens the risk of disability and mortality, over and above the risk from individual diseases (11,12,17,38–40). Particular pairs of chronic diseases are prevalent, and are synergistic in increasing risk for disability (38–40). For example, the concurrent presence of heart disease and osteoarthritis of the knee increased the relative risk of developing mobility disability to 13.6, from a relative risk of 4.4 for those with osteoarthritis alone, or 2.3 for those with heart disease alone (compared to those with neither disease) (40).

As shown in Figure 1, using the standard definition of comorbidity in the Cardiovascular Health Study data described above, the presence of two or more diseases can be shown to identify a different, though overlapping, subset of the population than does the definition of frailty or the definition of disability, in this case by difficulty in one or more ADLs. Overall, of the 368 participants (of 4317) who were frail, 27% reported disability in one ADL (with or without comorbidity) and 68% reported having two or more chronic conditions (with or without disability); 21% of those who were frail were also disabled and had comorbid disease (23). Thus, these definitions offer distinction of these conditions and evidence for their co-occurrence.

Recent work developed in clinical geriatrics suggests that comorbidity could be thought of as occurring at multiple physiologic/pathophysiologic levels, beyond just that of clinically diagnosed diseases. For example, researchers are increasingly evaluating the interactions of concurrently present impairments, such as strength and balance (41) or vision and hearing (Windham BG, et al. Unpublished observations), or biomediators, such as interleukin-6 and insulin-like growth factor-I (42), in contributing to downstream outcomes of frailty and disability. In fact, it is also possible that a clinical disease can be undiagnosed due to atypical or silent presentation or subclinical status, but contribute substantially to the burden of comorbidity. As a consequence of this work, we are starting to understand that current definitions of comorbidity based on diseases that are fully manifest should be revisited. If the value of considering comorbidity is capturing the synergistic interactions that lead to worsened outcomes than would be found from just the additive effects of the individual conditions alone, then comorbidity should, theoretically, involve interactions between any two conditions, even of clinical or subclinical

Table 5. Baseline Frailty Status Predicting Disability, Falls, Hospitalizations, and Death over 3 Years: Community-Dwelling Men and Women Aged 65 Years and Older, Cardiovascular Health Study

	Hazard Ratios* Estimated Over 3 Years Frail*** (Versus Not Frail)
Worsening mobility disability	1.50**
Worsening ADL disability	1.98**
Incident fall	1.29**
First hospitalization	1.29**
Death	2.24**

*Cox proportional hazards models, covariate adjusted (Ref. 17, reprinted with permission).

**$p \leq .05$.

***Frailty is defined as the presence of 3 or more characteristics among weight loss $\geq$10 lbs in past year, weak grip strength (lowest quintile), exhaustion (by self-report), slow gait speed (slowest quintile), and low physical activity (lowest quintile).
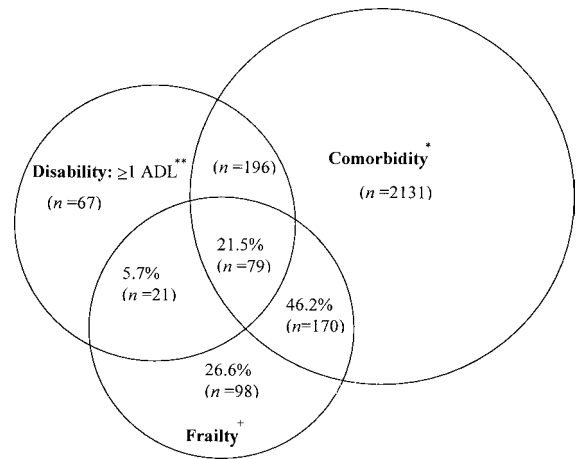
ADL = activity of daily living.

Figure 1. Prevalences—and overlaps—of comorbidity, disability, and frailty among community-dwelling men and women 65 years and older participating in the Cardiovascular Health Study (Ref. 23, reprinted with permission). Percents listed indicate the proportion among those who were frail ($n = 368$), who had comorbidity and/or disability, or neither. Total represented: 2762 participants who had comorbidity and/or disability and/or frailty. $^+n = 368$ frail participants overall. *$n = 2576$ overall with 2 or more of the following 9 diseases: myocardial infarction, angina, congestive heart failure, claudication, arthritis, cancer, diabetes, hypertension, chronic obstructive pulmonary disease. Of these, 249 (total) were also frail. **$n = 363$ overall with an activity of daily living disability; of these, 100 (total) were also frail.

diseases with impairments or physiologic biomediators. This issue leads to more questions than answers at this point. However, given that both comorbidity (38–40) and frailty (23) are independent risk factors for disability, perhaps at this time we can think about comorbidity as the aggregation of clinically manifest diseases present in an individual, and frailty as the aggregate of subclinical losses of reserve across multiple physiologic systems.

INTERRELATIONSHIPS OF DISABILITY, FRAILTY AND COMORBIDITY

Thus, as demonstrated epidemiologically (Table 5 and Figure 1), frailty is distinct from, but overlapping with, both comorbidity and disability. In addition, both frailty and comorbidity predict disability, adjusting for each other; disability may well exacerbate frailty and comorbidity, and comorbid diseases may contribute, at least additively, to the development of frailty. Early data from the Cardiovascular Health Study also suggest that the presence of disability or frailty could contribute to development or progression of chronic diseases, possibly through the lower activity levels associated with the former two conditions, or through other pathways affecting some basic biological mechanism essential to the maintenance of homeostasis, such as inflammation, or sympathetic–parasympathetic equilibrium (25,26). These causal relationships provide explanation for the frequent co-occurrence of these conditions, and suggest the clinical importance of differentiating them so as to identify appropriate interventions that could prevent one condition, given that its precursor is present.

Thus, there are causal interrelationships that can help explain why these three entities are likely to co-occur. A clinical manifestation of this co-occurrence is the high likelihood of finding a greater proportion of frail persons among those who are disabled than among the nondisabled; this is supported in data from the Women's Health and Aging Study, in which 28% of this moderately to severely disabled population of women aged 65 years and older living in the community were frail, compared to 7% of

a healthier subset of older women in the Cardiovascular Health Study (Boyd CM, et al. Unpublished observations).

THE COMPLEXITY OF MEDICAL CARE FOR PATIENTS WITH COMORBIDITY, FRAILTY, AND/OR DISABILITY

Why should we care clinically that not all frail patients are disabled, not all disabled patients are frail, and comorbidity may or may not be present with these? One reason is that comorbidity, frailty, and disability each confer specific care needs in older patients (see Figure 2), and the complexity of health care needs and necessity for coordination of care among multiple providers and services increases with the number of these conditions present. The second is that prognosis differs for each condition. We address, first, the treatment issues for each condition, independently, as a basis for describing the additive complexity when multiple conditions are present, and then address prognosis.

Regarding patients with *comorbid conditions*, it is recognized that specialized care focused on a single disease can lead to inadequate attention to other illnesses present (43). Beyond recognition and treatment appropriate for each condition, there can be complications due to competition or clinical interactions between conditions. Evidence-based protocols for treatment of a given disease may indicate the use of medication and treatment regimens that may be beyond the patient's tolerance or ability to comply due to other comorbid diseases that are present, as when dementia (or depression) can limit ability to adhere to treatments selected for other diseases (43,44). The treatment for one disease can also adversely affect the other, as in the case of antidepressant or vasodilator medications that may increase fall risk (45,46), or the use of nonsteroidal antiinflammatory

```
┌─────────────────────────────┐        ┌──────────────────────────────────────────┐
│  A. Physical Health Concerns│        │   B.   Major Health Care Implications      │
│       for Older Adults      │        │                                            │
└─────────────────────────────┘        └──────────────────────────────────────────┘
```

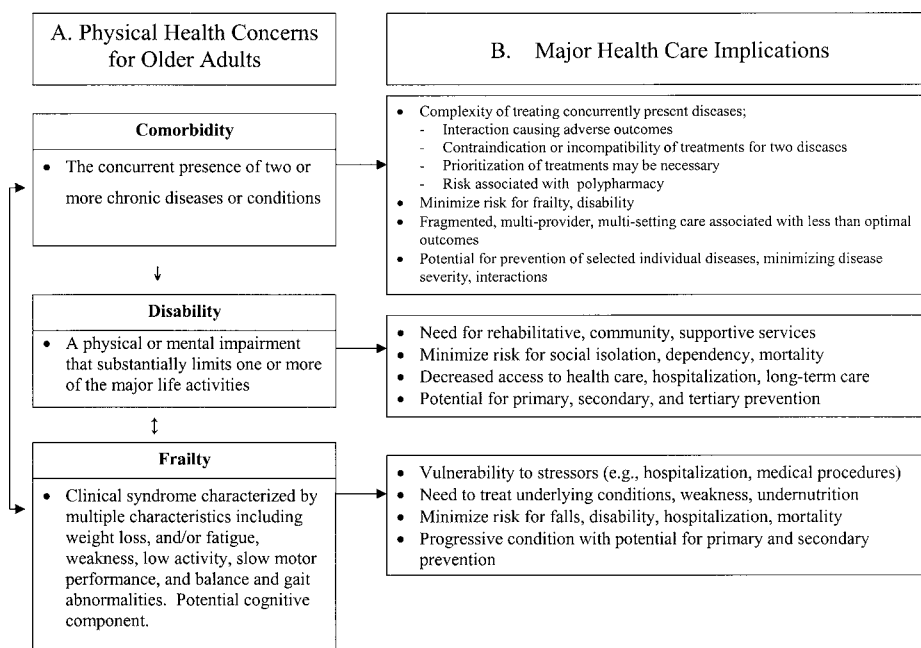| A. Physical Health Concerns for Older Adults	B. Major Health Care Implications

Comorbidity
 	
• The concurrent presence of two or more chronic diseases or conditions
	• Complexity of treating concurrently present diseases;
	  - Interaction causing adverse outcomes
	  - Contraindication or incompatibility of treatments for two diseases
	  - Prioritization of treatments may be necessary
	  - Risk associated with polypharmacy
	• Minimize risk for frailty, disability
	• Fragmented, multi-provider, multi-setting care associated with less than optimal outcomes
	• Potential for prevention of selected individual diseases, minimizing disease severity, interactions

Disability • A physical or mental impairment that substantially limits one or more of the major life activities	• Need for rehabilitative, community, supportive services • Minimize risk for social isolation, dependency, mortality • Decreased access to health care, hospitalization, long-term care • Potential for primary, secondary, and tertiary prevention
Frailty • Clinical syndrome characterized by multiple characteristics including weight loss, and/or fatigue, weakness, low activity, slow motor performance, and balance and gait abnormalities. Potential cognitive component.	• Vulnerability to stressors (e.g., hospitalization, medical procedures) • Need to treat underlying conditions, weakness, undernutrition • Minimize risk for falls, disability, hospitalization, mortality • Progressive condition with potential for primary and secondary prevention

Figure 2. Comorbidity, disability, and frailty: definitions and major health care implications. Theoretical pathway showing the relationships between comorbidity, disability, and frailty and summarizing the health care implications of each condition.

drugs to treat arthritis, which could also exacerbate gastritis (47). In some cases, it may be necessary to prioritize the diseases requiring treatments because all those indicated may not be feasible, simultaneously, for the patient. In another variant of this issue, in patients with poor short-term prognoses due to other health conditions, it may be inappropriate to implement treatments recommended by clinical guidelines for a given condition because the patient is unlikely to experience any short-term benefit from a treatment (as, perhaps, in use of statins in a patient with a terminal illness) (48). In each of these situations, clinical attention to these dynamics between comorbid diseases could improve overall outcomes and decrease adverse sequellae, as well as minimize medical regimens that may be unlikely to improve outcomes within the patient's life expectancy. Overall, in the face of comorbidity, the care of patients becomes predictably complex.

Medical care for *disability* heavily involves rehabilitation to minimize compromised function, regain function, or prevent further decline. The patient may be unable to ambulate or drive, or may need assistive devices or human assistance in the home or outside activities, and community services such as transportation to health care or "Meals on Wheels." Disabled older adults are also at risk for other adverse outcomes such as social isolation, dependency, and the need for long-term care, each necessitating appropriate interventions. When patients are disabled, needs for medically related services increase while their ability to navigate the health care system without help may decrease. Care of disabled older adults, often in the setting of comorbid diseases, requires coordination of medical care among multiple providers, and services to compensate for losses in function—such as meal provision—to maintain the

patients in their homes. Finally, decreased activity resulting from disability might increase risk for onset of new chronic diseases or initiation of frailty.

Frail patients also appear to have specific care needs, beyond care of underlying or coincident comorbidities and associated disability, as above. Medical care for frail older adults needs to include ruling out, and treatment of, pathologic causes of progressive weakness, weight loss, decreased exercise tolerance, slowed task performance (i.e., walking speed), and/or low activity. Underlying diseases that could be causing secondary frailty could range from depression to congestive heart failure, hypothyroidism, or tumors (21). Treatment should include attention to minimizing further loss of weight, muscle mass, and strength, which are hallmarks of frailty and risk factors for resulting disability. Randomized trials indicate that even the frailest nursing home patients can benefit from resistance exercise, with almost two-fold increases in lean body mass and resulting improvements in strength, exercise tolerance, and walking speed, and even greater improvements with the addition of nutritional supplements (49). Additionally, frail older adults clinically appear to have lower ability to tolerate stressors such as medical procedures or hospitalization (Boyd CM, et al. Unpublished observations), which may place them at risk for disability or other adverse outcomes, relative to others their age. Rehabilitation of frail older patients with disability presents special challenges. Frailty is characterized by wide fluctuations of health status and high risk of acute complications (e.g., infection) that can interrupt, multiple times, the recovery program, negatively impact the functional progress, and greatly increase the health care cost. Intensive and frequent medical surveillance of these patients, aimed at preventing acute fluctuations in health status, may allow

more effective rehabilitation and strongly affect the prognosis of these patients. These observations may warrant screening to identify frail older adults, so as to minimize risk from such stressors, to prevent adverse outcomes for which a frail older adult is vulnerable, including decompensation with acute illness or injury, falls, hospitalization, disability, and mortality, or to intervene quickly to prevent a spiral of physiologic decline.

It is not uncommon for older adults to concurrently have comorbid diseases and be frail and/or disabled. The frequency, illness burden, and limitations associated with having these multiple conditions are exemplified by the representative sample of moderately to severely disabled, community-dwelling women aged 65 to 101 years who participated in the Women's Health and Aging Study I (Table 1) (50). In this cohort, 74% reported difficulty walking 2 to 3 blocks and 15% were homebound. They had an average of 4.3 chronic diseases and 28% were frail. This population is at high risk of social isolation due to sensory and mobility impairments (11). Observing all of the health issues simultaneously at play in these disabled older women in the community offers insight into the complex health care needs for this population. They also highlight the simultaneous necessities to minimize the severity of multiple chronic diseases, promote the maintenance of function, and prevent further frailty, functional decline, and loss of independence. These simple data also exemplify some of the issues for disabled older adults that can lead to difficulty in organizing or traveling to health care, such as mobility and sensory decrements. Thus, in this subset of community-dwelling older adults, the care of patients becomes quite complex.

PROGNOSTIC IMPLICATIONS OF FRAILTY, COMORBIDITY, AND DISABILITY

Each of these three conditions has serious prognostic implications independent of the others. Each condition is also independently associated with increased health care needs and costs, including hospitalization risk (18,23,37, 51,52). When two of these health conditions are present, there can be additive or synergistic effects on health costs and utilization. This is demonstrated by analyses we conducted of the 2455 persons aged 65 years and older assessed in the Medical Expenditure Panel Survey 1996 data (a national random survey of 22,061 Americans) (53), assessing the relationship of health care utilization and cost with number of chronic conditions (none vs two or more) and with a standard, joint measure of disability and functional limitations. As shown in Table 2, costs for inpatient care and medications for older adults with two or more chronic conditions and a disability were five-fold greater than for those with disability alone, and over two-fold greater than for those with comorbidity alone. There are similar relationships for rates of hospitalization and number of prescription drugs, while use of home care occurs almost exclusively among those with *both* comorbidity and disability (53). These findings give additional weight to the argument that comorbidity and disability, while having distinct and important influences on the health of older adults, also have aggregate effects.

OPPORTUNITIES FOR PREVENTION

Another important reason for distinguishing the three conditions is mounting evidence that each is preventable, but requiring different interventions. Based on evidence that physical disability in older adults is preventable (11,12, 49,54), disability prevention, with attendant screening, diagnosis, and treatment, has entered the province of primary care providers as well as the rehabilitation specialist. Screening older adults for those at high risk of disability (7,8,10) and for reversible risk factors (11,12) may identify persons who would benefit from specific interventions. Many chronic diseases—such as cardiovascular disease—also are preventable into the oldest ages, and thus comorbidity can also potentially be diminished. Frailty, as well, has potential for prevention, both from the evidence above regarding resistance exercise being effective in increasing lean body mass (49), and because new evidence indicates that frailty is a progressive condition that begins with a preclinical stage (23), thus offering opportunities for early detection and prevention.

IMPORT OF DIAGNOSIS AND TREATMENT OF EACH OF FRAILTY, COMORBIDITY, AND DISABILITY

An individual can be experiencing, simultaneously, multiple symptoms of comorbid diseases, difficulty doing valued or necessary ADLs, and the progressive weakness and vulnerability associated with frailty. As shown above, they may also cause or exacerbate each other. For example, disability may limit ability to access, or comply with, health care, and thus lead to an increase in unrecognized and untreated health needs. Additionally, decreased activity or nutritional intake due to disability could increase risk of specific diseases or of frailty. The causal interconnectedness of these conditions, as well as their co-occurrence, makes diagnosis and treatment of each condition that is present important to improving overall health outcomes for older adults. Clinical outcomes for these patients will likely benefit from improving our ability to differentiate these entities and target therapies.

Health status evolves as people age, and the health care needed evolves as well. With the accumulation of these three composite conditions affecting health outcomes in an aging population, the complexity of health status associated with two or three of these conditions concurrently being present can lead to the need for multiple health care providers, caregivers, and community services, and to rapid changes in health status over time. Together, these necessitate effective coordination of care between providers or sites of care. The challenge to the physician and to the health care system generally, in caring for these complex patients, should not be underestimated (see Figure 2). Future research needs to build on this evolving ability to distinguish disability, frailty, and comorbidity, to refine their definitions and criteria, to develop standardized approaches to screening and risk assessment, and to gain knowledge of interventions to prevent onset and adverse outcomes for each condition.

Address correspondence to Linda P. Fried, MD, MPH, Center on Aging and health and the Division of Geriatric Medicine and Gerontology, The Johns Hopkins Medical Institutions, 2024 E. Monument Street, Suite 2-700, Baltimore, MD 21205. E-mail: lfried@jhmi.edu

REFERENCES

1. Council on Scientific Affairs. American Medical Association white paper on elderly health. Report of the Council on Scientific Affairs. *Arch Intern Med.* 1990;150:2459–2472.
2. Hoffman C, Rice D, Sung HY. Persons with chronic conditions: their prevalence and costs. *JAMA.* 1996;276:1473–1479.
3. Wagner EH, Austin BT, Von Korff M. Organizing care for patients with chronic illness. *Milbank Q.* 1996;74:511–544.
4. Pope A, Tarlov A. *Disability in America: Toward a National Agenda for Prevention.* Institute of Medicine (U.S.) Committee on a National Agenda for the Prevention of Disabilities. Washington, DC: National Academy Press; 1991.
5. Adams PF, Hendershot GE, Marano MA. *Current Estimates from the National Health Interview Survey, United States, 1996.* (Vital and Health Statistics, Series 10, No. 200). Hyattsville, MD: National Center for Health Statistics; 1999.
6. Nagi SZ. Disability concepts revisited: implications for prevention. Institute of Medicine. *Disability in America: Toward a National Agenda for Prevention.* Washington, DC: National Academy Press; 1991:309–327.
7. Rubenstein LV, Calkins DR, Greenfield S, et al. Health status assessment for elderly patients. Report of the Society of General Internal Medicine Task Force on Health Assessment. *J Am Geriatr Soc.* 1989;37:562–569.
8. Applegate WB, Blass JP, Williamson TF. Instruments for the functional assessment of older patients. *N Engl J Med.* 1990;322:1207–1214.
9. Reuben DB, Herr KA, Pacala JT, Potter JF, Pollock BG, Semla TP. *Geriatrics at Your Fingertips.* 2002 Ed. Malden, MA: Blackwell Science, Inc., for the American Geriatrics Society; 2002.
10. Chaves PH, Garrett ES, Fried LP. Predicting the risk of mobility difficulty in older women with screening nomograms: the Women's Health and Aging Study II. *Arch Intern Med.* 2000;160:2525–2533.
11. Fried LP, Guralnik JM. Disability in older adults: evidence regarding significance, etiology, and risk. *J Am Geriatr Soc.* 1997;45:92–100.
12. Stuck AE, Walthert JM, Nikolaus T, Bula CJ, Hohmann C, Beck JC. Risk factors for functional status decline in community-living elderly people: a systematic literature review. *Soc Sci Med.* 1999;48:445–469.
13. Ferrucci L, Guralnik JM, Simonsick E, Salive ME, Corti C, Langlois J. Progressive versus catastrophic disability: a longitudinal view of the disablement process. *J Gerontol Med Sci.* 1996;51A:M123–M130.
14. Harris T, Kovar MG, Suzman R, et al. Longitudinal study of physical ability in the oldest-old. *Am J Publ Health.* 1989;79:698–702.
15. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med.* 1995;332:556–561.
16. Gill TM, Robison JT, Tinetti ME. Difficulty and dependence: two components of the disability continuum among community-living older persons. *Ann Intern Med.* 1998;128:96–101.
17. Fried LP, Kronmal RA, Newman AB, et al. Risk factors for 5-year mortality in older adults: the Cardiovascular Health Study. *JAMA.* 1998;279:585–592.
18. Anderson G, Knickman J. Changing the chronic care system to meet people's needs. *Health Affairs.* 2001;20:146–160.
19. Gabrel CS. An overview of nursing home facilities: data from the 1997 National Nursing Home Survey. *Advance data from vital and health statistics; no. 311.* Hyattsville, MD: National Center for Health Statistics; 2000.
20. Fretwell M. Acute hospital care for frail older patients. In: Hazzard WR, Bierman EL, Blass JP, Ettinger WHJ, Halter JB, eds. *Principles of Geriatric Medicine and Gerontology.* 3rd Ed. New York: McGraw-Hill; 1993:241–248.
21. Fried LP, Walston J. Frailty and failure to thrive. In: *Principles of Geriatric Medicine and Gerontology.* 5th Ed. Hazzard WR, Blass JP, Ettinger WH Jr, Halter JB, Ouslander J, eds. New York: McGraw-Hill; 2003:1487–1502.
22. Buchner DM, Wagner EH. Preventing frail health. *Clin Geriatr Med.* 1992;8:1–17.
23. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol Med Sci.* 2001;56A:M146–M156.
24. Lipsitz LA, Goldberger AL. Loss of "complexity" and aging. Potential applications of fractals and chaos theory to senescence. *JAMA.* 1992;267:1806–1809.
25. Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of subclinical cardiovascular disease with frailty. *J Gerontol Med Sci.* 2001;56A:M158–M166.
26. Walston J, McBurnie MA, Newman A, et al. Frailty and activation of inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Arch Intern Med.* 2002;162:2333–2341.
27. Morley JE, Perry HM, Miller DK. Something about frailty [editorial]. *J Gerontol Med Sci.* 2002;57A:M698–M704.
28. Morley JE. Testosterone replacement in older men and women. *J Gend Specif Med.* 2001;4:49–53.
29. Bortz WM. A conceptual framework of frailty: a review. *J Gerontol Med Sci.* 2002;57A:M283–M288.
30. Visser M, Pahor M, Taaffe DR, et al. Relationship of interleuking-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elder men and women: the Health ABC Study. *J Gerontol Med Sci.* 2002;57A:M326–M332.
31. Lipsitz LA. Dynamics of stability: the physiologic basis of functional health and frailty. *J Geronotol Biol Sci.* 2002;57A:B115–B125.
32. Cohen HJ. In search of the underlying mechanisms of frailty [Editorial]. *J Gerontol Med Sci.* 2000;55A;M706–M708.
33. Rockwood K, Hogan DB, MacKnight C. Conceptualisation and measurement of frailty in elderly people. *Drugs Aging.* 2000;17:295–302.
34. Ferrucci L, Guralnik JM, Studenski S, Fried LP, Cutler GB, Walston JD. Designing randomized controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: a consensus report. The Interventions on Frailty Working Group. *J Am Geriatr Soc.* In press.
35. *Dorland's Illustrated Medical Dictionary.* 30th Ed. Philadelphia: W B Saunders Co.; 2003.
36. Guralnik J, LaCroix A, Everett D, Kovar M. *Aging in the Eighties: The Prevalence of Comorbidity and It Association With Disability. Advance Data From Vital and Health Statistics.* Hyattsville, MD: National Center for Health Statistics; 1989.
37. Anderson G. Testimony before the Subcommittee on Health of the House Committee on Ways and Means. Hearing on Promoting Disease Management in Medicare; 2002: *http://waysandmeans.house.gov/health*
38. Fried LP, Bandeen-Roche K, Kasper JD, Guralnik JM. Association of comorbidity with disability in older women: the Women's Health and Aging Study. *J Clin Epidemiol.* 1999;52:27–37.
39. Verbrugge LM, Lepkowski JM, Imanaka Y. Comorbidity and its impact on disability. *Milbank Q.* 1989;67:450–484.
40. Ettinger WH, Davis MA, Neuhaus JM, Mallon KP. Long-term physical functioning in persons with knee osteoarthritis from NHANES. I: effects of comorbid medical conditions. *J Clin Epidemiol.* 1994;47:809–815.
41. Rantanen T, Guralnik JM, Ferrucci L, et al. Coimpairments as predictors of severe walking disability in older women. *J Am Geriatr Soc.* 2001;49:21–27.
42. Cappola AR, Xue QL, Ferrucci L, Guralnik JM, Volpato S, Fried LP. Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women. *J Clin Endocrinol Metab.* 2003;88:2019–2025.
43. Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. *N Engl J Med.* 1998;338:1516–1520.
44. Moroney JT, Tseng CL, Paik MC, Mohr JP, Desmond DW. Treatment for the secondary prevention of stroke in older patients: the influence of dementia status. *J Am Geriatr Soc.* 1999;47:824–829.
45. Rubenstein LZ, Josephson KR, Robbins AS. Falls in the nursing home. *Ann Intern Med.* 1994;121:442–451.
46. Rothschild JM, Bates DW, Leape LL. Preventable medical injuries in older patients. *Arch Intern Med.* 2000;160:2717–2728.
47. Scott DL, Berry H, Capell H, et al. The long-term effects of non-steroidal anti-inflammatory drugs in osteoarthritis of the knee:

a randomized placebo-controlled trial. *Rheumatology* (Oxford). 2000; 39:1095–1101.

48. Welch HG, Albertsen PC, Nease RF, Bubolz TA, Wasson JH. Estimating treatment benefits for the elderly: the effect of competing risks. *Ann Intern Med.* 1996;124:577–584.

49. Fiatarone MA, O'Neill EF, Ryan ND, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med.* 1994;330:1769–1775.

50. Guralnik JM, Fried LP, Simonsick EM, Kasper JD, Lafferty ME. *The Women's Health and Aging Study: Health and Social Characteristics of Older Women With Disability.* Bethesda, MD: National Institute on Aging, 1995; NIH Pub. No. 95-4009.

51. Wu S, Green G. *Projection of Chronic Illness Prevalence and Cost Inflation.* Rand PM-1144. Washington, DC: RAND; 2000.

52. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med.* 2002;162:2269–2276.

53. Household Component, 1996 Medicare Expenditure Panel Survey. Rockville, MD: Agency for Healthcare Research and Quality; 1996. *http://www.ahrq/dat/mepweb.htm*

54. Wagner EH, LaCroix AZ, Grothaus L, et al. Preventing disability and falls in older adults: a population-based randomized trial. *Am J Publ Health.* 1994;84:1800–1806.

Editor Nominations

Journal of Gerontology: Medical Sciences

The Gerontological Society of America's Publications Committee is seeking nominations for the position of Editor of the *Journal of Gerontology: Medical Sciences.*

The position will become effective January 1, 2005. The Editor makes appointments to the journal's editorial board and develops policies in accordance with the scope statement prepared by the Publications Committee and approved by Council (see the journal's masthead page). The Editor works with reviewers and has the final responsibility for the acceptance of articles for his/her journal. The editorship is a voluntary position. Candidates must be dedicated to developing a premier scientific journal.

Nominations and applications may be made by self or others, but must be accompanied by the candidate's curriculum vitae and a statement of willingness to accept the position. **All nominations and applications must be received by May 1, 2004.** Nominations and applications should be sent to the GSA Publications Committee, Attn: Jennifer Campi, The Gerontological Society of America, 1030 15th Street, NW, Suite 250, Washington, DC 20005-1503.