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Aging and frailty: Just a wrinkle in time.

Written by Lawrence M. Scheier, Ph.D. and Arbi ben Abdallah, Ph.D.

There is a quote, usually attributed to Benjamin Franklin, which reads "*Things as certain as death and taxes, can be more firmly believ'd.*" It was actually written by Daniel Defoe in 1726 as part of his opus "*The political history of the devil.*" Regardless of its rightful origins, we can add to his wonderful wisdom "*it is only natural that we all get old.*" Indeed, aging is very much a part of life, and as much as we try to fend off the untoward effects of getting old and retain our youthful fervor it will eventually come to us all. There is considerable popular commentary written in today's news about how vibrant (and connected) older people can be, using their smartphones or tablets to FaceTime grandchildren, running marathons way into their 80s, and joining various social and athletic clubs to stay active. Daily we read of exceptional elderly individuals either living way past their prime years on a diet of vodka and natural herbs or energetically climbing tall peaks or skydiving. These are precious moments and give us pause that with purpose and heart we too can enjoy our "sunset years" as a welcome stage in life.

However, all is not rosy as a short amble through a local nursing home or memory care facility will reveal. Many elderly individuals lack a certain "joie de vivre." Instead we find older adults that have lost their "grip" on life (literally) and with each passing day they struggle to recall fading memories and experience waning physical strength.



In the medical community, and among those tasked with caring for the elderly, standard markers that alert us to problems with older persons include trouble engaging normal daily activities (i.e. dressing, feeding, and bathing), limitations getting around (reduced mobility), problems engaging in normal activities and loss of interest in social activities. To the

observant family member the elderly person's daily routine is reduced to the basic functions in order to thrive. The term "*frailty*" is used to reference this global set of markers, indicating a lack of physiological reserve and diminished resistance to both internal and external stressors.

In this issue of the LARS eNEWS we briefly examine the concept of *frailty* and further explore its relations to surgical outcomes in elderly patients. As part of a collaboration, we examined data obtained from thousands of patients having surgical procedures in 2014, who consented to be part of an electronic medical registry and gathered preoperative data as well as post-discharge outcomes. We copiously mined these data to identify several proxy markers of frailty and empirically evaluated their predictive efficiency. Before we examine these new and exciting findings, we briefly explore how the aging and gerontological literatures define frailty and the common methods used to portray frailty.

Conceptual Models of Frailty. Frailty is at best a "fuzzy" construct with many different

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definitions and even different applications²⁻⁵. In primary care settings, physicians intuitively use the concept of frailty to gauge patients resolve, their health and robustness. Surgeons assess frailty to gauge the patient's resolve for post-operative recovery. However, there is no consensus how frailty should be measured or at heart what frailty genuinely represents⁵⁻⁶.

Most physicians will agree that frailty is not equated with age or disease and is not the same thing as disability⁷. Although its underlying pathophysiology remains obscure, frail elderly adults are vulnerable to disease and intrusive surgical interventions increase the risk of morbidity and can lead to mortality in some cases. It is for this reason that some have gone as far as to characterize frailty as the "elephant in the operating room."⁷

The medical literature clarifies frailty as a "complex system failure" owing to lack of system redundancies, where defenses are broken down one by one. The integration of the molecular, cellular, and physiologic systems that give vibrancy to our life become brittle and slow down leading to multi-systemic dysregulation. When this occurs, something as simple as ambulation, which requires higher cortical control, is made more difficult and frequent falls occur in frail persons often leading to long-term hospitalization or extended nursing care.

Fried et al.¹ suggested that frailty is a "state of high vulnerability for adverse health outcomes, including disability, dependency, falls, need for long-term care, and mortality" and considered it a distinct clinical "phenotype" that could be characterized using five core markers whose cumulative presence or absence indicate severity of frailty^{*8}. These five identifying criteria include involuntary weight loss, exhaustion, slow walking speed, poor handgrip strength and sedentary behavior (i.e., low physical activity).

When applied to community-dwelling older adults, there are many strengths to the phenotype approach[†]. Based on a critical mass of markers or symptoms, it is "coherent, reproducible and identifies frailty as a wasting disorder with sarcopenia as a key pathophysiological feature"³. However, this approach also has some drawbacks, in particular it does not assess cognitive functioning or mood and considers only

physical burdens. Moreover, the salience of the respective five criterion is never addressed, all receive equal weights in determining frailty. Studies now show that the prevalence of markers within phenotypes can vary considerably and also the predictive significance of each marker may vary with regard to health and disability outcomes⁹⁻¹⁰. Three of the five markers, handgrip strength, walking speed, and physical activity are measured on continuous scales and must be dichotomized using a 20th centile rule, necessitating a reference population.

In many cases, it is likely that a comprehensive geriatric assessment (CGA) would be needed to understand, for instance, why there was sudden weight loss or reduced grip strength and to better understand the underlying pathophysiology or metabolic etiology. At the very least, this would include assessing physical, cognitive, environmental, psychosocial and socioeconomic factors that can influence an older person's health¹¹.

The phenotype approach can be contrasted with the work of Rockwood and colleagues¹²⁻¹⁴ who proposed a "deficit accumulation model" of frailty. In their view, a proper assessment of frailty should include anywhere from 20-70 items and incorporate a mini-mental status examination, physical performance measures, clinical assessment of frailty, and a standardized geriatric assessment including activities of daily living, social, psychological, and neurological deficits. This more expansive assessment is required to make valid clinical decisions regarding elderly patients and orchestrate successful interventions. As an algorithm, the Frailty Index is calculated as the proportion of deficits from the total (rescaled to 0-1), enabling the clinician to use a wide range of measures with different markers.

Interestingly, Rockwood and colleagues showed that it does not matter whether you use the five specific Fried markers of physical burden or randomly choose 10 from the 70 they had available you still get the same cumulative density distribution for individuals classified as frail vs. robust¹⁵.

Research Findings. Regardless of conceptual approach, the geriatric literature shows there is considerable importance to assessing frailty. It is related to falls in the elderly¹⁶⁻¹⁷, length of hospitalization or nursing home stay¹⁸, surgical



outcomes¹⁹⁻²¹, post-operative complications²², quality of life²³ and predict health outcomes including disability, morbidity and mortality in patients with cardiovascular disease²⁴ and cardiac surgery risk surgery²⁵⁻²⁶. In some cases, research studies have used frailty indicators to predict five-year survival outcomes²⁷ and even mortality^{20, 27-28}. A recent expert consensus meeting²⁹ encouraged geriatricians to include cognitive impairment and measures of neuropsychological functioning in their frailty assessments. This led to a proliferation of both "screeners"³⁰ and more comprehensive instruments to assess frailty³¹⁻³³.

Rothman and colleagues³⁴ augmented the Fried criteria with measures of depression and cognitive impairment and were able to predict chronic disability, long-term nursing home stays (> 4 months), falls, and death in over 700 community dwelling elderly adults (>70 years). Interestingly, slow gait speed, low physical activity and weight loss were efficient predictors as was cognitive impairment; however, self-reported exhaustion and muscle weakness did not inform future health outcomes.

Avila-Funes and colleagues³⁵ added cognitive impairment to the five Fried criteria in a four-year prospective study of French elderly (65-90). They found a higher proportion of cognitively impaired elderly that met criteria for "frail," and that frail older persons with cognitive impairment were almost twice as likely to be hospitalized, five times as likely to have incident dementia and more likely to develop task-related and functional disability.

Research on Typologies of Frailty. Several investigators have now applied classification strategies to determine the validity of the Fried phenotype approach. Liu and colleagues³⁶ obtained three classes of frailty based on physical burden markers used with elderly Taiwanese adults. They labeled the three

* This is done by categorizing the continuous index ranging from 0-5 into robust (no criteria), pre-frailty (one or two criteria) and frailty (three or more).

† The work of Fried and colleagues was based on the Cardiovascular Health Study.

classes healthy normal, mobility (marked by slowness and weakness), and non-mobility (weigh loss or exhaustion) groups. Elderly assigned to the mobility class were at much greater risk for mortality and poor health outcomes. Bandeen-Roche and colleagues³⁷ used Latent Class Analysis and found support for the Fried 3-class phenotype. They noted that both frail and intermediate frail women were at much greater risk for mortality, incident IADL and ADL disability and nursing home entry, compared to non-frail women.



Item Response Theory and LCA Methods Applied to Frailty. Our own research has shown that we can develop a reliable and valid “screener” of frailty. Using data from an electronic medical registry (~N=3,000), we used item response theory to identify a “continuum or liability” of frailty. We began with 32 proxy markers representing physical health (7), emotional (7), nutrition and weight loss (3), fitness and functional (11), and social support (4) domains. We then pruned these down to 18 markers and used latent class analysis to derive meaningful subtypes of frailty. Following derivation of subtypes, we then examined associations between patients’ class membership and surgical outcomes.

LCA Findings. A 3-class model fit the data well; with slightly under one-half of the patients not endorsing items above the .60 threshold. These patients were assigned to the “Not Frail” class. About a third were assigned to the “Moderately Frail” class because they endorsed poor physical quality of life, slow performance of physical activities, limited function in moderate ADLs, accomplishing less because of physical or emotional problems, and limited in climbing flights of stairs above the proscribed .60 benchmark.

The remaining patients were labeled “Severely Frail” because they endorsed 12 frailty markers across the physical, functional limitations, and emotional health domains, all exceeding the designated threshold. These included 2 of the physical health domain items, five of the functional limitation items, and all five of the emotional health markers.

Regression Models. We then examined relations between class membership and post-operative complications, hospital readmission

within 30 days of discharge, and self-reported quality of life using multivariable logistic regression. These models controlled for various comorbidities and potential confounders as well as demographic covariates. Both Moderately and Severely Frail patients were more likely to have post-operative complications (compared to Not Frail). Both groups were also more likely to be readmitted (compared to the Not Frail). Finally, Moderately Frail and Severely Frail patients were less likely to report worsening quality of life compared to the Not Frail patients.

Summary of Findings. We found that 18 markers of frailty efficiently indicated an underlying “liability” of frailty. These markers represented four domains, considerably expanding on the physical burden markers used in the Fried Index. When these markers were examined using classification techniques, we obtained three distinct classes that differed in their severity of frailty. After assigning patients to their respective classes, we found that they differed on their health conditions (e.g., comorbidities) and surgical risk. Furthermore, those assigned to the Severely Frail class were at greater risk for readmission and complications compared to the Not Frail.

Parting Thoughts. The idea behind developing a valid and reliable assessment of frailty is that it can be used to identify individuals at risk for poor outcomes (i.e., disability or mortality). With this information in hand, practitioners can formulate an appropriate intervention and policy experts can streamline resources to those most in need. The idea of using a practical, efficient, and valid screener of frailty has been the focus of several intervention studies that use exercise and physical activity to stave off disability³⁹⁻⁴¹. Along these lines, there is also some indication that reducing smoking, which is a powerful inflammatory stimulus, could be one route to reduce frailty. Others include reducing abdominal obesity through exercise and nutritional changes, the latter which can also help to reduce systemic metabolic failures that contribute to frailty. Resistance exercise training lends itself to increasing lean body mass as will sound nutritional practices targeting caloric and protein intake, and include vitamin supplements. These are vital steps to prevent further functional decline in the frail elderly⁴².

It should be clear that prevention is very valuable in these cases “if” we can develop a reliable and valid instrument that has clinical utility, the instrument is shown to be sensitive and specific, and can be implemented in a clinical setting without too much burden to both patient and physician⁴³. This is perhaps impetus for the recent emphasis on developing

an easy and quick screening tool for detecting frailty⁴⁴⁻⁴⁵. An important point to make about frailty is that it can be caught early and at the very least can be attenuated or reversed before it spirals into a cascade of disease or worse results in some form of disability that necessitates hospitalization or extended nursing home stay.

Regardless of conceptual approach, the markers that indicate frailty should be the focus of clinical intervention in the elderly. As clinicians are well aware, many diseases have unknown etiology, but can still be treated. Frailty, with its multi-systemic and heterogeneous etiology, may just fit that bill.



This study also demonstrates it is essential that physicians and other allied health professionals should gain access to electronic medical records in order to use the information contained therein to make clinically valid decisions regarding treatment. Whether information is required for a pre-surgical evaluation or utilized in deciding the optimal course of action as part of a therapeutic regimen (even pharmacokinetics), the plethora of information contained in these records can improve diagnostic accuracy and, as a result can support targeted prevention as well as intervention strategies. One thing is certain, however, and that is keeping active, retaining the desire to engage in activities, being mobile, and socializing with others are all good remedies to stave off the symptoms of frailty and for some even death.



Postscript. Dr. Scheier would like to dedicate this work to the people living at the Philadelphia Geriatric Center located at the corner of York and Olney Streets. He is forever grateful for their wisdom and the precious time

the residents spent with him talking informally about the inevitability of growing old. Furthermore, this work would not have been

possible without the tutelage and mentorship of Powell Lawton (deceased), who was a terrific muse, a wonderful scientist, and a giant

in the field of gerontology and geriatric medicine.

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15029 N. Thompson Peak
Parkway
Suite B111-443
Scottsdale, AZ 85260