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Moving Frailty Towards Clinical Practice: NIA Intramural Frailty Science Symposium Summary

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Abstract

Frailty has long been an important concept in the practice of Geriatric Medicine and in Gerontological Research, but integration and implementation of frailty concepts into clinical practice in the US has been slow. The National Institutes of Aging (NIA) Intramural program and

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the Johns Hopkins Older Americans Independence Center sponsored a symposium in order to identify potential barriers that impede the movement of frailty into clinical practice and in order to highlight opportunities to facilitate the further integration of frailty into clinical practice. Primary and subspecialty care providers, and investigators working to integrate and translate new biological aging knowledge into more specific preventive and treatment strategies for frailty provided the meeting content. Recommendations included: a call for more specific language that clarifies conceptual differences between frailty definitions and measurement tools; the development of randomized, controlled trials to test whether specific interventions strategies for a variety of conditions differently affect frail and non-frail individuals; development of implementation studies and therapeutic trials aimed at tailoring care as a function of pragmatic frailty markers; the use of deep learning and dynamical systems approaches to improve the translatability of findings from epidemiological studies; and the incorporation of a advances in aging biology, especially focused on mitochondria, stem cells, and senescent cells, toward the further development of biologically targeted intervention and prevention strategies that can be used to treat or prevent frailty.

Keywords

Frailty; Clinical Practice; Geroscience

INTRODUCTION:

Over the past 20 years, the geriatrics literature has witnessed a proliferation of research focused on frailty. Early publications set out a variety of conceptual frameworks for frailty as a state of vulnerability with its own identity and clinical relevance, and reported the development and validation of diagnostic criteria[1–3]. As greater awareness of frailty as a clinical entity took root outside of Geriatric Medicine, methods of assessment rapidly proliferated. Most were developed to assess risk in older adults about to undergo invasive medical or surgical procedures, for complex care planning, or to establish goals of care [4]. Although several frailty detection instruments effectively identify patients at elevated risk for adverse health outcomes in a wide variety of subspecialty care settings [5], there remains a lag in the development of specific alterations care plans for frail patients in many, if not most, of these settings. Recently, movement towards integration of frailty into general clinical practice has come from United Kingdom (UK) based recommendations for the use of frailty detection tools to identify and manage frail patients using comprehensive geriatric assessment (CGA), and for targeted interventions using exercise and nutritional strategies [6–10].

Despite this progress, frailty assessment has not yet entered into routine primary or subspecialty clinical practice in the United States and in many other countries around the world. Furthermore, there remains a relative paucity of evidence that assessing frailty facilitates clinical decision-making and ultimately improves specific relevant outcomes for frail, older patients. To identify strategies that accelerate the integration of frailty into clinical practice and to stimulate the production of scientific evidence that supports such integration, a symposium was organized by the Intramural Program of the National Institutes

on Aging in collaboration with the Johns Hopkins Older Americans Independence Center leadership in September of 2017. The goals of this meeting were to: 1) identify barriers preventing more rapid integration of frailty assessment and interventions into clinical practice in the US; 2) uncover gaps in evidence that demonstrate effectiveness of interventions that are moving into practice and 3) use this information to inform the development of a future research agenda that will help to accelerate the integration of frailty into clinical practice in the US.

To maintain the focus on these specific goals, many important frailty-related topics that already have seen considerable discussion in the literature were not addressed in this symposium. Nor was a consensus on the definition of frailty sought. Rather, speakers were charged with identifying the highest-priority barriers and gaps to be surmounted, and with providing frailty research recommendations around 3 major themes detailed below.

I) Translating Frailty Into Clinical Practice: Barriers and Opportunities

Several major barriers and related opportunities to improve frailty integration into clinical practice were identified:

1) The lack of general consensus on the language used to describe frailty, and the differing theories on the nature of frailty, present ongoing barriers to researchers and may discourage clinicians considering using frailty assessment in clinical practice. Much of the delay in deploying frailty assessment methodologies, and in gathering relevant evidence to support the efficacy of intervention strategies, stems from the confusion as to what frailty is and how it can be best captured by a specific assessment. The lack of clarity may be connected in part by the use of the word ‘frailty’ to indicate disparate conceptual frameworks, risk predictors, and assessments. Furthermore, related—and as of now, loosely defined—concepts of ‘vulnerability’ and ‘resiliency’ have further confused clinicians and researchers alike. Given the long standing debate on these definitions and related terms, the organizers did not debate these topics or attempt a consensus. Rather they sought to move the field beyond this debate through recommending the development of clearer definitions as described below.

a. Clarification of Conceptual Frameworks for Commonly Utilized Frailty Models:

The two most highly cited frameworks that have emerged in the literature both carry the label of ‘frailty’ despite marked differences in their theory and conceptual basis, respective methods for assessment, and identification of frail individuals by each method when applied to the same sample of people [11;12] (figure 1). The first concept, often termed “physical” or “phenotypic” frailty, has been defined as “a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, causing vulnerability to adverse outcomes [2].” Its biologic basis is thought to be implicated primarily, and quite specifically, through altered stress response systems and energy metabolism

abnormalities. Its clinical hallmarks of weakness, slowness, weight loss, fatigue, and low activity were derived from clinical observations of older adults who were declining. These core features were hypothesized to be proxies of manifestations of dysregulation in specific physiologic domains. The second major concept, often termed "deficit accumulation," hypothesized that the accumulation of health and functional problems serves as an indicator of an individual's aging-related health state[1]. This concept has been operationalized into a "frailty index" assessment, which does not include pre-specified variables but suggests assessing a wide range of potential signs, symptoms, laboratory abnormalities, medical conditions, social settings and disabilities, among others. In this concept, each deficit is not considered individually or differentially as imparting increased risk for mortality, but thought to reflect, at high levels of accumulated co-morbidity, a higher risk for mortality than expected given one's chronological age. Both assessment methods have proven useful for identifying vulnerable older adults at higher risk for mortality.

In addition to these two common conceptual frameworks, a third aims explicitly to identify a "pre-disability"[13] state; many others incorporate disability, age, cognition, and psychosocial domains. Frailty assessments that bundle multiple other geriatric outcomes together in their measurement introduce additional ambiguity: how to distinguish a frailty diagnosis from a cognitive decline, the presence of disability or any other of the components that comprise the assessment. Further, it was highlighted that the identification of frailty may be most useful for prevention purposes if it is identified before the development of disability and related cognitive and functional decline.

b. Recommendations for Clarity in Labeling Frailty and Related Terms

The development of broadly accepted consensus-driven guidelines that discriminate distinct conceptualizations of frailty, provides better labeling, and determining how to most appropriately utilize each of them in clinical practice was recommended as an opportunity. Developing such guidelines would provide clarity for clinicians and researchers seeking to implement through frailty assessment. For example, labeling types of frailty with more specific and descriptive terms could be helpful. This more detailed 'naming' of frailty would include the use of '**syndromic** frailty' or '**physical** frailty' ascertained through the phenotyping method described above; alternatively '**deficit accumulation** frailty' would be recommended for frailty based on counting co-morbidities and disabilities. These more specific terms would immediately clarify how 'frailty' was ascertained, and also point towards potential clinical utility of the type of frailty. For example, if 'deficit accumulation frailty' was measured, then interventions targeting specifically identified and treatable co-morbidities could be

considered, and studies could be designed to evaluate the effectiveness of these interventions. In contrast, if 'physical frailty' is identified, then biological mechanisms hypothesized, and then evidenced, as etiological could be targeted in preventive or treatment strategies. Finally, the terms 'resiliency' (or lack of it) and 'vulnerability' are often confused conceptually with frailty and should also be better defined as they move towards clinical practice. NIA or Geriatric Medicine Organization working groups on these topics could provide additional clarification and naming guidelines in the coming years.

2) Detection of frailty in individual patients has not yet been linked to any broadly applied medical or pharmacological treatment. Frailty, moreover, has not yet been identified by FDA as a condition deemed treatable with a drug. Clinicians in this session suggested that chronic medical conditions such as depression or congestive heart failure are more likely to be monitored and followed in clinical practice if there are established diagnostic and/or treatment strategies. The continuation of efforts to gain FDA approval for pharmacological agents targeting the biology that underlies physical frailty and sarcopenia, remains an ongoing goal and recommendation from the group [14]. In order to pursue more rigorous FDA approval opportunities, further development of research programs that improve knowledge of the biological etiologies of frailty and at the same time informs the development of more meaningful preventive and treatment strategies were strongly recommended.

3) To date, few randomized controlled studies have evaluated the effectiveness of assessing frailty for improving health outcomes in clinical practice, or the associated cost-benefit tradeoffs. Although there has been some movement of frailty measurement into clinical practice as described above, there is a general lack of knowledge about what interventions or alterations in care plans are truly efficacious in frail older adults: further effort to envision benefits that might be possible, develop strategies to achieve these benefits, and then rigorously evaluate their efficacy and safety through randomized, controlled study is needed. There is also a need to clearly distinguish different roles of frailty in the design, conduction and interpretation of intervention studies. For example, frailty could be considered as an outcome to be prevented or ameliorated in its own right, or as a marker to identify subgroups of older adults who respond differentially to interventions for specific medical conditions. Work is needed to define what clinical outcomes are most relevant for these studies, with emphasis on patient preferences. Furthermore, time-consuming frailty assessments were highlighted as potential impediments to achieving favorable cost- and time-benefit ratios and to routinely implementing frailty assessment in clinical practice. Development of short screening tools and the evaluation of their potential use as an entrée into more formalized frailty assessment was advocated, as was the need for studies to evaluate the specificity and sensitivity, validity, and predictive ability of the shorter screens compared with well-validated, lengthier counterparts. With an expanding older population, finally,

and a commensurately expanding subpopulation of frail older adults, evaluation of frailty interventions for their cost-benefit will be needed. There has been relatively little investigation to date in this important area, particularly in the realm of prevention and primary care.

II) Integration of Frailty into Subspecialty Practice:

The implementation of frailty assessment for risk stratification in subspecialty practice has been at least partially successful but there is still little evidence to support broad screening of frailty across these specialties. In addition, fewer specific individualized clinical interventions were developed based on frailty status, and therefore the process of decision making in the presence of a frailty diagnosis is still subjective, with little support from scientific evidence. The following section discusses results of these conversations and the need for further research in these areas.

1. Frailty Assessment in Subspecialty Practices May Encourage Further Development: Four potential benefits to frailty assessment in advance of clinical procedures, as an adjunct to clinical risk predictors, were identified. Firstly, studies that evaluated frailty assessment as a means to target interventions have often shown that frail individuals benefit as much or more from many types of intervention than non-frail individuals, and therefore should not be excluded from these interventions [15;16]. Secondly, in situations where frail individuals are susceptible to experiencing adverse events subsequent to treatments, alteration of care plans to recognize and address frail status can help guide care in a safer direction for frail older adults, for example, the choice of transcatheter aortic valve replacement (TAVR) over standard of care [17]. Thirdly, rehabilitation or prehabilitation that includes exercise therapy, nutritional supplementation, or a walking program to improve disability is likely to be beneficial for patients who are found to have physical frailty [7;18]. Related recommendations from comprehensive geriatric assessment (CGA) in those identified as frail may improve procedure outcomes through improved medical care and rehabilitation strategies before performing higher risk interventions [9;18].

2. Inclusion of Frailty Assessment in Clinical Studies: There was broad agreement that frail older adults should be included in clinical studies that target frailty per se and the conditions that frail, older adults are likely to develop. In addition, adding frailty assessment as components of any clinical study targeting older adults, and utilizing already existing data sets to better understand the impact of frailty on treatments or outcomes could be helpful. As discussed above—and reiterated by speakers in this session—few interventions specifically addressing frailty or incorporating frailty assessment have been robustly tested in large multicenter clinical trials. Assuming that high risk patients can be identified through frailty assessment, the development of frailty specific treatment plans remain a critically important research need. A diagnosis of frailty may also guide the development of management plans that maximize access to beneficial treatments and services by highly vulnerable (or frail), while at the same time avoiding interventions that may provide no benefits in this specific patient group. Similarly, forecasting the functional consequences of a major surgical intervention, and contrasting these with the natural history of the underlying disease, enables patients and families to make more informed decisions.

3. Considerations of Frailty Diagnosis as a Stratification Factor or Condition for Treatment: An important distinction in the handling of a frailty diagnosis is whether frailty is considered: 1) a stratification factor that orients the treatment plan and allows the evaluation of whether certain treatments are similarly or differently effective in frail versus non-frail individuals or 2) a condition that can be prevented, slowed down or even reversed. Before being recommended for use, any potential intervention that might distinguish treatment of older adults based on their frailty status will require studies to demonstrate effectiveness in improving patient centered outcomes, followed by additional studies to determine cost effectiveness, and passive surveillance to demonstrate effectiveness in real world settings. Similarly, evidence will be needed to demonstrate that any frailty assessment method proposed for clinical stratification has incremental prognostic value above established clinical predictors, or value for guiding the use of specific care pathways, treatment strategies, or frailty interventions that lead to improved outcomes.

In studies reporting clinical applications of frailty assessment, frailty indices, frailty phenotypes, and frailty estimated by clinical judgment have all been utilized, along with many new, discipline-specific frailty assessment measures [4;5]. Many tools were developed for the setting of an acute illness or an urgent surgical or medical intervention—necessarily, considering that traditional measures of frailty may not be feasibly assessed in acutely decompensated situations. Proliferation of such frailty assessments may be helpful for risk stratification and for medical decision making, but could also lead to further confusion in light of debates as to frailty conceptualization and measurement, as discussed in section I. It was noted, moreover, that no available frailty assessment was designed to optimally succeed at such risk-stratification, and that research to develop optimal risk predictors specific to a wide variety of clinical settings may be needed.

4. Potential Use for Diffusion of Innovation Theory for Frailty Research: Given the rapidly growing number of publications on frailty in the subspecialty literature, the *Diffusion of Innovation Theory* was discussed as potentially applicable for rapid deployment of relevant frailty measurement and tested interventions once clinical solutions are developed and tested. According to this theory, new ideas and strategies are brought out by *innovators*, received by *early adopters of innovation*, accepted by an early majority who adopt innovations, and finally implemented by those who are slow to adopt changes [19]. Enlisting effective partners from the sub-specialties in this process would be particularly important, because their stakeholders will be the ones who drive acceptance of innovations as useful, effective, and feasible in their greater clinical organizations [20].

III. Using Basic Science Discovery Related to Improve Clinical Practice Related to Frailty

NIA's Geroscience initiative, which seeks to connect the biology of aging to susceptibility to frailty, disease, functional and cognitive decline, and multi-morbidity, and ultimately to translate these findings into novel clinical prevention and treatment strategies, is thought to have a high potential to influence clinical practice related to frailty. Given the marked complexity and multifactorial biological etiologies of frailty, opportunities to utilize new methodologies borrowed from bioengineering and life course studies were also highlighted.

1. Geroscience Initiative and Frailty: The 'Geroscience Initiative' stems from the recent gains in understanding aging-related molecular mechanisms and the relatively slow pace of efforts to translate these findings into clinical practice that improves health-span and prevents of frailty [21]. Biological mechanisms related to age-related changes in telomeres, epigenetic regulation, proteostasis, metabolic derangements, mitochondrial function, cellular senescence, and stem cells biology[22] and their possible links to frailty were considered. Although many of these areas hold promise for identifying possible determinants of frailty, few direct causal links to frailty have to date been identified. Despite this, the further development of biological discovery related to frailty, and downstream discovery related to diagnostic, preventive, and treatment strategies was considered an important ongoing and future opportunity to engage clinicians to diagnose and treat frailty.

2) Multisystem Etiology Development: Mitochondrial function decline, cellular senescence, and stem cell dysfunction were identified as being among the biological domains where intervention development is moving forward and may hold relevance for the prevention or treatment of frailty [23–25]. Indeed, many studies have already demonstrated that altered markers of stress response and energy metabolism are closely related to physical frailty [26–29]. The role of declines in multiple biological and physiological systems as etiological determinants of frailty was also considered, with focus on systems that broadly influence the entire organism rather than specific organs and that could potentially be targeted in clinical practice. Although these pathways have to date mostly been studied in isolation, it was highlighted that the development of integrated approaches are needed that assume that intervening on critical biological hubs may be more effective that targeting specific biomarkers per se.

3) Recommendations for Integration of Bioengineering Strategies into Frailty Research: Promisingly, techniques of data discovery and mathematical modeling—largely borrowed from engineering [30], such as artificial intelligence and dynamical systems analysis—are beginning to be applied to understand the role of multisystemic decline in frailty. For example, the human body might be conceptualized as a machine made up of complex parts—here, the molecular systems or physiological systems listed above—which are integrated into a mutually interacting, stably performing whole. In younger age groups, or in a robust older state, all of the mechanical systems work well together. In frailty, however, aging-related changes in multiple components of the human 'machine' break down or wear out with increasing frequency, as does the network of interactions and intercommunication channels. As that happens, other systems may be damaged and deteriorate, leading to increasing dysregulation and high risk for systemic failure of the entire machine. In this model, the early identification of key machine components or intercommunication channels that are eroding may be crucial to developing effective diagnostic strategies and treatments for frailty.

Building on this theory, the potential ability to identify one "gateway" system (e.g. the inflammatory / innate immune system), whose balance is critical to all the rest, and that could be an intervention target was discussed. Alternatively, consideration was also given to the possibility that there may be no gateway system, and that interventions directed to

multiple aspects of the physiological network will be needed. Current recommendation for the treatment of hypertension provides a good example of this approach; the use of multiple drugs that act on different biological pathways are utilized to impact the condition rather than just the underlying biology per se. The possibility for individualized diagnostic and treatment planning based on measured biology was discussed as an area requiring further research, with the acknowledgement that success in this domain could revolutionize the way that older adults are diagnosed and treated for frailty.

4) Need for Life course Study of Frailty-Related Biology—A pressing need to understand life course trajectories in the context of frailty research was also expressed, as was the need to acquire knowledge of the biological pathways that are most impacted by environmental variables/stressors. Doing so may be key to identifying biological pathways that have the most interventional relevance. Developing preventive strategies than minimize the impact of these stressors or maximize individuals' resilience to these stressors over the life course may provide the biggest impact on population health. Implicit in this thinking is that cellular changes come first, followed by physiological and then phenotypic changes, followed by the emergence of functional changes and disease states. By the time that functional decline and disease states emerge, biological and phenotypical mechanisms may be beyond repair. This further highlights the need for new research on biological mechanisms in order to intervene early in the course of the evolution of frailty. Finally, specific interventions, treatments and translation were envisioned in the context of precision medicine. Measuring biological responses to stressors rather than in a static state may indeed be the only way to identify early dysregulation in relevant biological systems. Research into physical resiliency using stress response paradigms to ascertain such new measurements is now an active area of research that may well produce insights for novel biological measurements, diagnostic strategies, and treatments targeting frailty.

SUMMARY:

The goal of this symposium was to identify barriers that prevent more rapid integration of frailty into clinical practice, to uncover gaps in evidence that demonstrate effectiveness of interventions that are moving into practice and to use this information to inform the development of the next generation of frailty research focused on clinical practice integration. Five of the main considerations and recommendations were abstracted by the authors from the meeting content and are synthetically summarized in Table 1.

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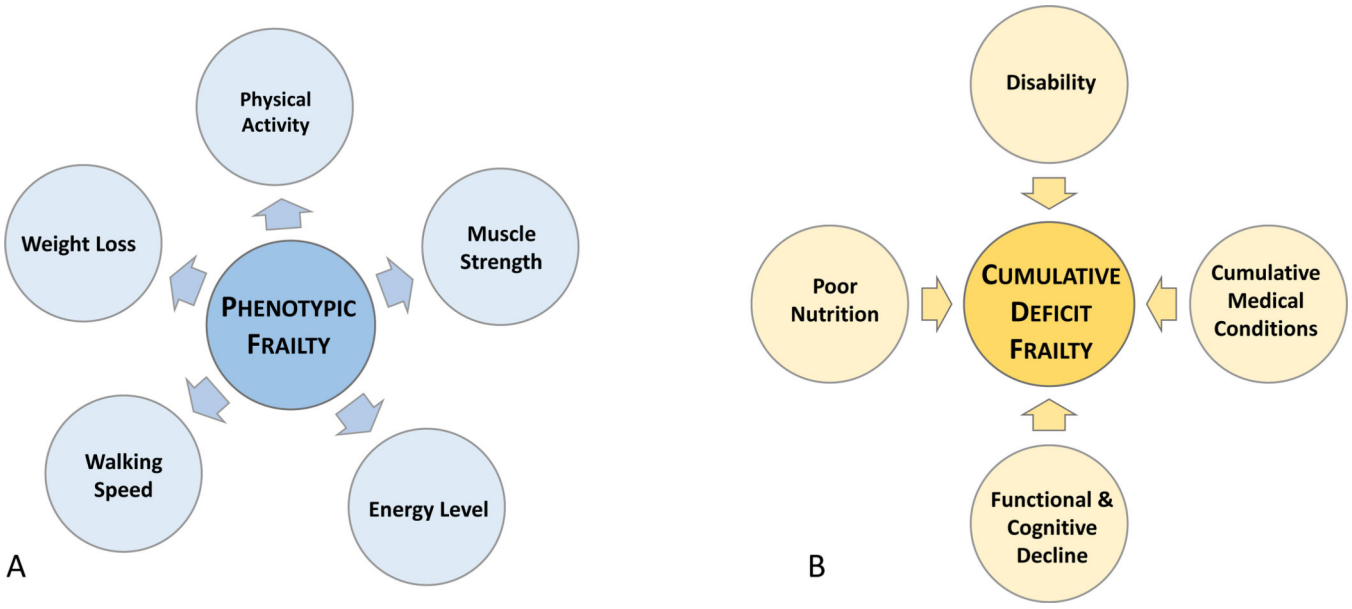

Figure 1:

Representation of conceptual framework of two major theories on frailty. Phenotypic frailty (A) also referred to as physical or syndromic frailty, is hypothesized to have a specific age-related biological basis that drives the appearance of signs and symptoms (outward pointing arrows). Cumulative deficit frailty (B) is hypothesized to be driven by cumulative, non-specific health, functional, psychological and cognitive deficits (inward pointing arrows). Both concepts of frailty predict vulnerability to adverse outcomes and have led to multiple derivative frailty detection tools.

Table1:

Summary of 5 major points derived from symposium with resulting recommendations

1	**Broad use of generic term "frailty" to capture both conceptualization and measurement confuses clinicians and investigators and further slows integration into clinical practice.** *Work across research field to use more specific language that will help to differentiate frailty concepts and measures.*
2	**The slow integration of frailty measurement in clinical practice is likely due to lack of clinical studies that demonstrate clear benefit and/or related clinical recommendations for older adults.** *Develop randomized, controlled studies of specific intervention strategies stratified by frailty standards and develop studies targeting frailty "per se".*
3	**Subspecialists have made progress in the development of frailty-related risk assessment tools, but few have developed specific clinical recommendations based on frailty status.** *Develop implementation studies and therapeutic trials aimed at tailoring care as a function of pragmatic frailty markers.*
4	**NIA's Geroscience initiative has focused the need to integrate new knowledge of aging biology into frailty research and towards translation into diagnostic, preventive and treatment strategies.** *Develop key biological studies that focus on mitochondrial biology, stem cells, and cellular senescence would likely be of highest yield.*
5	**Evidence suggests that broad age-related changes in physiological stress response systems and energy metabolism contribute to frailty.** *Utilization of deep learning and dynamical systems approaches and the development of interventions that target specific system components may facilitate the diagnosis and treatment of frailty.*

Bold= Summary Statement *Italics*= Recommendation