Geriatric Syndromes: Clinical, Research, and Policy Implications of a Core Geriatric Concept

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(See Editorial Comments by Dr. William Hazzard on pp 794-796)

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The term "geriatric syndrome" is used to capture those clinical conditions in older persons that do not fit into discrete disease categories. Many of the most common conditions that geriatricians treat, including delirium, falls, frailty, dizziness, syncope and urinary incontinence, are classified as geriatric syndromes. Nevertheless, the concept of the geriatric syndrome remains poorly defined.

Although heterogeneous, geriatric syndromes share many common features. They are highly prevalent in older adults, especially frail older people. Their effect on quality of life and disability is substantial. Multiple underlying factors, involving multiple organ systems, tend to contribute to, and define, geriatric syndromes. As noted previously,¹ frequently, the chief complaint does not represent the specific pathological condition underlying the change in health status. In some cases, the two processes may involve distinct and distant organs, with a disconnect between the site of the underlying physiological insult and the resulting clinical symptom. For example, when an infection involving the urinary tract precipitates delirium, it is the altered neural function in the form of cognitive and behavioral changes that permits the diagnosis of delirium and determines many functional outcomes. The fact that these syndromes cross organ systems and discipline-based boundaries, along with their multifactorial nature, challenges traditional ways of viewing clinical care and research.

The concept of a geriatric syndrome has already facilitated the development of multicomponent intervention strategies and the establishment of "V" codes through the Centers for Medicare and Medicaid Services for falls history. Nevertheless, the lack of a working definition has limited the usefulness of this term in the clinical, research, and policy arenas. Such a definition should seek to encompass the overarching clinical features that have led clin-

Geriatricians have embraced the term "geriatric syndrome," using it extensively to highlight the unique features of common health conditions in older people. Geriatric syndromes, such as delirium, falls, incontinence, and frailty, are highly prevalent, multifactorial, and associated with substantial morbidity and poor outcomes. Nevertheless, this central geriatric concept has remained poorly defined. This article reviews criteria for defining geriatric syndromes and proposes a balanced approach of developing preliminary criteria based on peer-reviewed evidence. Based on a review of the literature, four shared risk factors—older age, baseline cognitive impairment, baseline functional impairment, and impaired mobility-were identified across five common geriatric syndromes (pressure ulcers, incontinence, falls, functional decline, and delirium). Understanding basic mechanisms involved in geriatric syndromes will be critical to advancing research and developing targeted therapeutic options, although given the complexity of these multifactorial conditions, attempts to define relevant mechanisms will need to incorporate more-complex models, including a focus on synergistic interactions between different risk factors. Finally, major barriers have been identified in translating research advances, such as preventive strategies of proven effectiveness for delirium and falls, into clinical practice and policy initiatives. National strategic initiatives are required to overcome barriers and to achieve clinical, research, and policy advances that will improve quality of life for older persons. J Am Geriatr Soc 55:780-791, 2007.

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icians to apply this term to seemingly diverse conditions. Moreover, little progress has been made in developing a mechanistic understanding of common geriatric syndromes, with no agreement on how such research should be conducted.

The goals of this article are to describe the advantages and limitations of establishing formal criteria for geriatric syndromes, to evaluate shared risk factors across five distinct geriatric syndromes, to propose potential mechanistic approaches for conducting basic-to-clinical translational research into geriatric syndromes, and to discuss local and national efforts to translate geriatric syndrome research to practice and policy. It is hoped that this article will help to catalyze further development in the field of geriatric syndromes—in the clinical, research, and policy domains.

THE DEVELOPMENT OF FORMAL CRITERIA FOR GERIATRIC SYNDROMES

The conceptualization of geriatric syndromes has been evolving over time.² In general terms, a "syndrome" has been defined as "a group of signs and symptoms that occur together and characterize a particular abnormality"³ or "the aggregate of symptoms and signs associated with any morbid process, and constituting together the picture of the disease."^{2,4} Thus, in current medical usage, a syndrome refers to a pattern of symptoms and signs with a single underlying cause that may not yet be known⁵ (Figure 1).

Geriatric syndromes, by contrast, refer to "multifactorial health conditions that occur when the accumulated effects of impairments in multiple systems render [an older] person vulnerable to situational challenges."⁶ Thus, the geriatric usage of the term "syndrome" emphasizes multiple causation of a unified manifestation.^{2,5} With this usage, the conceptualization of geriatric syndromes aligns itself well with the concept of "phenotype," defined as "the observable characteristics, at the physical, morphologic, or biochemical level, of an individual, as determined by the genotype and environment."⁴ This concept emphasizes the multiple contributors to observable characteristics, such as the frailty phenotype.⁷

Geriatric syndromes pose some special clinical considerations. First, for a given geriatric syndrome, multiple risk factors and multiple organ systems are often involved. Second, diagnostic strategies to identify the underlying causes can sometimes be ineffective, burdensome, dangerous, and costly. Finally, therapeutic management of the clinical manifestations can be helpful even in the absence of a firm diagnosis or clarification of the underlying causes.

Are there alternative options for terminology? Rather than "geriatric syndrome," alternative terms might be "final common pathway" or "end product." In this conceptualization, the geriatric syndrome represents the result of a series of processes or changes, suggesting multiple contributors. This conceptualization parallels other medical conditions such as renal failure and hypertension, to which multiple causes may contribute, for which it may not always be appropriate to search for underlying cause(s), and for which management does not always depend on the underlying cause(s).

Establishing formal criteria to define syndromes has a long tradition in medical research and practice. Examples include criteria within rheumatology to define rheumatoid arthritis⁸ and systemic lupus erythematosus,⁹ the National

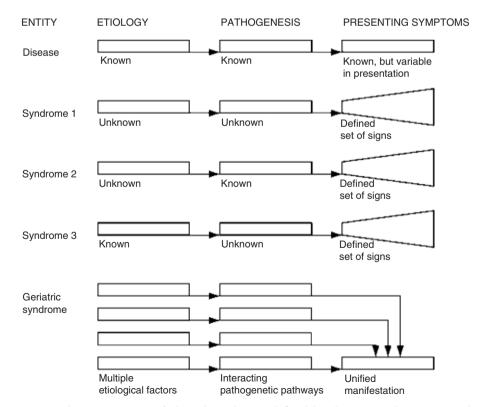


Figure 1. Schematic conceptual representation of clinical conditions defined by the terms "disease," "syndrome," and "geriatric syndrome," illustrating differences in numbers and complexity of relevant factors, including etiological risk factors, pathophysiological mechanisms, and presenting symptoms. Adapted with permission from Olde Rikkert et al.⁵

Institute of Neurological and Communicative Diseases and Stroke-Alzheimer's Disease and Related Disorders Association clinical criteria for Alzheimer's disease,¹⁰ and psychiatric diagnoses in the Diagnostic and Statistical Manual of Mental Disorders.¹¹ The advantages of such criteria include improved communication in clinical and research settings, enhanced ability to directly compare syndromes between studies and to pool study findings, and the ability to create International Classification of Diseases codes and billable diagnoses. The development of formalized criteria will also assist with creating unified concepts to facilitate pathophysiological studies and enhance the search for common mediators. For areas such as delirium and chronic fatigue syndrome, operational definitions have been developed that have facilitated research in these areas. Despite these advantages, premature establishment of formal criteria-without an adequate evidence base-can create rigid conceptualizations, stymie development and progress within the field, and lead to inappropriate application of concepts by clinicians and researchers with the potential for inaccurate diagnosis and therapeutic mismanagement. Examples of this phenomenon include the premature classification of diabetes mellitus as type I and type II or the hyperlipidemias as types I-V, which held back inquiry and progress for many years.

A balanced approach would be to develop preliminary criteria for select geriatric syndromes with an adequate evidence base by working committees assembled by professional organizations such as the American Geriatrics Society (AGS). These preliminary criteria can be sent out for comment from other organizations and the AGS membership. Once published, these criteria could be regularly updated and allowed to evolve over time. For research studies, these criteria would be helpful to compare research samples and results; to pool study findings; to modify, expand, or focus study samples; and to appropriately target interventions.

SHARED RISK FACTORS FOR DISTINCT GERIATRIC SYNDROMES

A defining feature of geriatric syndromes is that multiple risk factors contribute to their etiology.³ Previous work has suggested that some geriatric syndromes might share underlying risk factors.⁶ A unifying conceptual model for geriatric syndromes is proposed (Figure 2), demonstrating that shared risk factors may lead to these syndromes and to the overarching geriatric syndrome of frailty. Although there is not yet a consensus definition, frailty is defined here as impairment in mobility, balance, muscle strength, cognition, nutrition, endurance, and physical activity.¹² Frailty and the other geriatric syndromes may also feedback to result in the development of more risk factors and more geriatric syndromes. These pathways in turn lead to the final outcomes of disability, dependence, and death. This conceptual model provides a unifying framework and holds important implications for elucidating pathophysiological mechanisms and management strategies.

Although each geriatric syndrome is distinct, it was hypothesized that they would have shared risk factors. Thus, a systematic review of the medical literature designed to examine previously identified risk factors for some com-

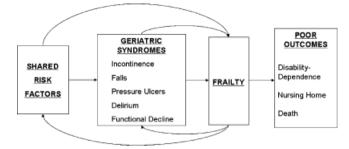


Figure 2. A unifying conceptual model demonstrates that shared risk factors may lead to geriatric syndromes, which may in turn lead to frailty, with feedback mechanisms enhancing the presence of shared risk factors and geriatric syndromes. Such self-sustaining pathways may result in poor outcomes involving disability dependence, nursing home placement, and ultimately death, thus holding important implications for elucidating pathophysiological mechanisms and designing effective intervention strategies.

mon geriatric syndromes and to identify common risk factors across all of these syndromes was conducted. Five geriatric syndromes were selected for this investigation, based on the following criteria; they are common, associated with a high degree of morbidity, demonstrated to be preventable in some cases, and investigated with multiple previous risk factor studies. The five geriatric syndromes investigated were pressure ulcers, incontinence, falls, functional decline, and delirium.

METHODS

A systematic review of the medical literature was conducted using PubMed from January 1990 through December 2005. The search was performed using key words and synonyms for each geriatric syndrome and the terms "risk factor" or "predictor." Abstracts were reviewed and articles selected based on indications that they were original articles that identified independent risk factors or a predictive model for the geriatric syndrome. Risk factors from each article were classified, and common risk factors across geriatric syndromes were identified.

RESULTS

For pressure ulcers, 12 recent risk factor studies were identified, 13-25 as summarized in Table 1. For incontinence, nine recent risk factor studies were identified.²⁶⁻³⁴ Risk factors present in at least two studies were older age (generally ≥ 65), high body mass index, functional impairment, impaired mobility, cognitive impairment or dementia, and use of physical restraints. For falls, 12 recent risk factor studies were identified.^{21,28,35–44} Risk factors present in at least two studies were older age, prior history of falls, functional impairment, use of a walking aid or assistive device, cognitive impairment or dementia, impaired mobility or low activity level, and balance abnormality. For functional decline, 12 recent risk factor studies were identified.^{21,45-55} Risk factors present in at least two studies were older age, previous falls, functional impairment, cognitive impairment or dementia, hospitalization, incident vascular event, depression, vision impairment, diabetes mellitus, and impaired mobility. For delirium, 36 risk factor

Reference	Age*			Impaired Mobility*	Low Weight	Nutrition	Diabetes Mellitus	Cognitive. Impairment*†	Functional Impairment*	Other
13				Х				х		Previous pressure ulcers
14	Х	Х		Х				Х		Cardiovascular disease or sepsis
15		Х				Х	Х			Anemia
16	Х		Х	Х				Х		
17	Х				Х	Х			Х	Female
18	Х	Х								Surgery
19				Х		Х		Х		Male, moisture, friction
20			х	Х	Х					White, fecal incontinence admitted from hospital
21	Х			Х	Х	Х			Х	Male, poor physical condition
22	Х					Х	Х	Х		Medical conditions
23	Х			Х		Х				Emergent admission
24				Х	Х					Nonblanchable erythema dry skin, lymphopenia
25	Х			Х		Х		Х		Hypotension, fever

Table 1. Risk Factors for Pressure Ulcers Based on a Systematic Literature Review

Note: Literature review from January 1990 through December 2005.

* Shared risk factors across geriatric syndromes.

[†]Includes decreased sensory perception.

studies were identified.^{56–89} Risk factors present in at least two studies were older age, cognitive impairment or dementia, psychoactive medication use, severe illness or multiple comorbidity, azotemia or dehydration, functional impairment, alcohol abuse, infection, metabolic derangement, and impaired mobility. Shared risk factors identified consistently across all geriatric syndromes in this study were older age, functional impairment, cognitive impairment, and impaired mobility. Although some risk factors (e.g., falls, diabetes mellitus) occurred across multiple geriatric syndromes, only the four identified risk factors occurred across all of the geriatric syndromes examined.

IMPLICATIONS

This study has confirmed the multifactorial etiology of the common geriatric syndromes of pressure ulcers, incontinence, falls, functional decline, and delirium. Four shared risk factors have been identified across all of these geriatric syndromes: older age, cognitive impairment, functional impairment, and impaired mobility. These findings raise the possibility of shared pathophysiological mechanisms across these syndromes, such as multisystem dysregulation, inflammation, sarcopenia, and atherosclerosis. Three of these four risk factors are amenable to intervention, such as through preventive strategies to provide reorientation for cognitive impairment or exercise, balance training, and mobilization to reduce functional impairment and impaired mobility. Testing of unified intervention strategies targeted toward these shared risk factors may prevent these common geriatric syndromes and frailty, along with their associated poor long-term outcomes.

PATHOPHYSIOLOGY OF MULTIFACTORIAL GERIATRIC SYNDROMES

The research community can point to many accomplishments achieved by a bench-to-bedside translational approach,^{90,91} which has been most impressive when addressing inborn errors of metabolism.⁹² At the same time, there has been a growing awareness that optimum clinical care cannot be based entirely on a biological framework.^{1,93–95} This observation is particularly pertinent to the management of geriatric syndromes, for which it is imperative also to consider relevant social, spiritual, and economic domains. Although it is difficult to study the pathophysiology of complex multifactorial geriatric syndromes, such studies must be undertaken if there is to be any chance at altering the natural history of these core contributors to late-life disability.

The pathophysiology of many nongeriatric conditions can be viewed along a traditional linear model (Figure 3A). For example, a genetic alteration can lead to a disease process involving one organ system. In other cases, a clinical cluster of diseases involving multiple organ systems may develop.⁹⁶ Although the term "syndrome" has been applied to genetic conditions with a multiorgan phenotype, the linear model is still applicable, because a direct relationship exists between altered genetics and the clinical phenotype.96 Nevertheless, this linear model does not lend itself well to the study of common diseases such as diabetes mellitus, hypertension, atherosclerosis, and cancer, which can only rarely be attributed to a single gene alteration. Moreover, this model also fails to incorporate the types of nonbiological considerations discussed above. The concentric model (Figure 3B) has been proposed as a means of highlighting the complexity of oncogenesis, together with

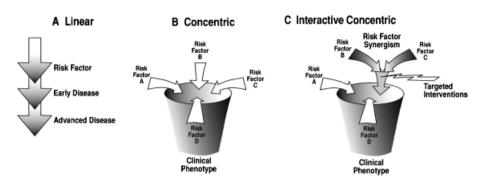


Figure 3. Mechanistic research addressing the pathophysiology of complex multifactorial geriatric syndromes will require the development of new conceptual models. The traditional linear model (A) has proven highly effective for the discovery of pathophysiologically relevant mechanisms in conditions such as inborn errors of metabolism, yet it does not adequately capture the multifactorial nature of geriatric syndromes. Cancer researchers developed the concentric model (B) as a means of designing more-effective cancer treatments by targeting multiple distinct oncogenic pathways.⁹⁷ This approach may also not be suitable for geriatric syndromes, because interventions targeting only one risk factor would address only a small portion of the overall risk for such conditions, whereas multicomponent pharmaceutical interventions risk being unfocussed and could lead to adverse effects typically associated with geriatric polypharmacy. An interactive concentric model (C) is proposed as a means of reconciling the need for mechanistic research with the conditions' multifactorial complexity by focusing on pathways associated with risk factor synergisms, thus offering a locus for the design of targeted interventions. Modified from Decker and Sausville.⁹⁷

the belief that the targeting of multiple pathways contributing to tumor survival and growth will improve treatment outcomes.⁹⁷ It is likely that this model can be adapted to study the pathophysiology of geriatric syndromes, because it permits the incorporation of the multifactorial complexity inherent in these conditions.

The above model is also attractive in that it permits the pathophysiology of geriatric syndromes to be addressed in a manner that reflects the complex interactions between an individual's vulnerabilities and exposure to specific challenges. Even young individuals and robust older individuals will fall, will develop cognitive deficits, or will become incontinent if challenged with a sufficiently great force, anticholinergic dose, or physical restraint. Frailty, falls, delirium, and incontinence research is starting to capture the nature of such enhanced vulnerability. For example, multiple risk factors, including sedative use, cognitive impairment, lower extremity disability, palmomental reflex, abnormalities of balance and gait, and foot problems, all enhance the risk of falls.98 The risk increases linearly with the number of risk factors in the model, ranging from 8% for none to 78% in the presence of four or more risk factors.⁹⁸ Although this has led to innovative efforts incorporating multicomponent elements into strategies for the prevention of key geriatric syndromes,^{99,100} it has been difficult to conceptualize pathophysiological studies to investigate such complex multifactorial conditions or to envision biologically based treatments that could alter their natural history.

Traditional translational research is poorly suited to address the pathophysiology of geriatric syndromes. First of all, it is possible to undertake careful research without establishing cause and effect, because simple correlations between molecular changes and clinical outcomes may not establish causality, even when demonstrated prospective-ly.¹⁰¹ In many ways, the use of genetically modified animals (largely mice) has revolutionized the conduct of research designed to address the pathophysiology of complex conditions, such as osteoporosis^{102,103} and Alzheimer's dis-

ease¹⁰⁴ by linking the presence or absence of a gene to a specific phenotype. These technological advances have led to a great increase in the use of mice in such research. For example, PubMed citations using mice to study osteoporosis increased 25-fold from 1975–1985 to 1995–2005, whereas mouse studies relevant to Alzheimer's disease increased 50-fold. Such approaches will continue to grow, because approximately 10,000 of the nearly 25,000 genes in the mouse genome have already been deleted with knockout mouse mutations, and many other mutations are expected to become available in the near future.¹⁰⁵

Nonetheless, attempts to define the pathophysiology of complex multifactorial geriatric syndromes using current approaches can be problematic. For example, a decision to focus all efforts on a single risk factor may lack geriatric relevance, because it addresses only a small portion of the overall risk and fails to consider other risk factors. By contrast, any research attempt to address all relevant risk factors runs the risk of being unfocused. Moreover, unlike the use of multicomponent behavioral strategies for prevention, multicomponent strategies involving many biological interventions targeting different pathways could lead to unacceptable adverse effects in frail older people, given the well-established risk of polypharmacy in this population.¹⁰⁶ If strategies for altering the natural history of common geriatric syndromes are to be developed, it will be essential to reconcile the need for defining relevant mechanisms with the underlying multifactorial complexity.

In spite of the enormity of the task, several promising directions need to be explored. One strategy involves capitalizing on the fact that some interventions exert highly specific effects on restricted populations of cells, whereas the effects of other strategies are more "pleiotropic," involving sometimes-varying effects across many different cells and tissues. Examples of such potentially beneficial pleiotropic interventions include hormones, statins, and antioxidants, as well as behavioral modifications such as exercise, improved nutrition, and weight loss. Not only is it essential to test such interventions, it is also imperative to explore the basic mechanisms by which each exerts effects that are both pleiotropic and beneficial in the context of specific geriatric syndromes. Although few investigators have pursued the development of animal models of individual geriatric syndromes, such a possibility should not be summarily dismissed. For example, the vulnerability of commonly used inbred mouse strains such as C57BL6J to develop a specific phenotype has been used in osteoporosis, diabetes mellitus, and atherosclerosis research.^{107,108} More recently, it has become apparent that the pattern of aging may vary greatly between different strains and that individual strains may exhibit a vulnerability to developing phenotypic features typical of geriatric syndromes, such as sarcopenic obesity.¹⁰⁹

Another approach involves an evaluation of the interactions between different risk factors in what could be termed the interactive concentric model of geriatric syndrome pathophysiology (Figure 3C). Investigators are beginning to identify interactive synergisms between different risk factors for individual geriatric syndromes. For example, one study has shown that the combination of low insulin-like growth factor-1 and high interleukin-6 levels in the same individual confers a higher risk for progressive disability and mortality in older women in a manner that suggests the presence of interactive synergisms between these two risk factors.¹¹⁰ It remains to be seen whether insulin-like growth factor-1 and interleukin-6 are actual mediators of relevant biological effects or markers of some other process. Nevertheless, these findings may have important clinical implications. The presence of such synergy implies that the pathways by which each of these risk factors contributes to progressive disability may biologically interact. The presence of such biological overlap between distinct risk factors (shaded arrow in Figure 3C) may offer unique opportunities for making sense of this complexity and for identifying priority targets for developing clinically useful interventions.

Detrusor muscle loss, fibrosis, and axonal degeneration in human bladder biopsies^{111,112} define detrusor underactivity, a multifactorial geriatric condition that contributes to urinary retention in frail older people.¹¹¹ In animal studies using genetically modified mice, macrophage migration inhibitory factor, an atypical and abundant uroepithelial cytokine, has been implicated in the pathways by which two different risk factors—urinary retention/outlet obstruction¹¹³ and lack of estrogen¹¹⁴—mediate bladder muscle loss and fibrosis. Moreover, aging, as well as comorbidities such as urinary tract infections,¹¹⁵ may also mediate their effects on detrusor underactivity via this pathway. Thus, it may be possible to use preclinical animal, as well as theoretical, models in an effort to define the efficacy of interventions designed to target such shared pathways in geriatric syndromes, analogous to the methods used by oncologists to anticipate the effects of drug combinations.¹¹⁶

LINKING GERIATRIC SYNDROME RESEARCH TO PRACTICE AND POLICY

Although research on geriatric syndromes has helped to clarify risk factors and to establish effective intervention strategies, the results based on this evidence have mostly failed to translate into clinical practice. The translation of

geriatric syndrome research into practice faces unique challenges, which may heighten the barriers to evidence-based implementation.¹¹⁷ Beyond the complex nature of geriatric syndromes, numerous factors pose barriers to dissemination, including the lack of commonly accepted definitions for the recognition, diagnosis, and coding of geriatric syndromes; the lack of simple, measurable interventions; the need for substantial provider time and longitudinal followup to intervene and assess effectiveness (i.e., intervention for geriatric syndromes requires human capital, rather than simply a new drug or technology); the frequent requirement for new behaviors or attitude shifts on the part of the patient or the provider(s) (e.g., working with interdisciplinary teams or focusing on identifying contributors such as urinary tract infection or drugs rather than ordering a brain scan for a delirious patient) and for system-wide changes across extended systems of care with coordination across multiple disciplines; the lack of champions for these interventions, particularly in the face of many other competing clinical demands and mandates; and the fact that the multifactorial nature of the geriatric syndromes-requiring a coordinated, multifaceted approach-does not adhere to the traditional disease model that drives most medical practice.94

In this section, the evidence–practice gap will be examined for two common geriatric syndromes: delirium and falls. Two examples of local efforts to translate research into practice for these conditions will be highlighted, along with the barriers to dissemination. Finally, a description of national efforts to link research to practice through policy initiatives will be provided.

Delirium

Overview

Delirium, defined as an acute decline in attention and global cognitive functioning, is a common and life-threatening problem for hospitalized older patients. Occurring in 14% to 56% of patients, delirium is associated with hospital mortality rates of 22% to 76%.¹¹⁸ Despite its clinical importance, delirium is unrecognized in 66% to 70% of patients¹¹⁹ and is documented in the medical record of only 3% of patients when present.¹²⁰ This lack of recognition has precluded effective intervention for delirium. Several recent intervention trials^{99,121–124} have documented that 30% to 40% of delirium may be preventable and that intervention may also reduce delirium duration.

Intervention Strategy and Dissemination Process

The Hospital Elder Life Program (HELP) has been demonstrated to be effective for prevention of delirium and functional decline^{99,125} and to be cost-effective for acute hospital costs¹²⁶ and long-term nursing home placement.¹²⁷ Moreover, a HELP dissemination site demonstrated reduction in delirium rates and hospital costs in a quality-improvement study.¹²⁸ Since 1999, the HELP Dissemination Program has been established to facilitate the translation of research into practice by providing assistance with the implementation of HELP at other hospitals. Interested sites purchase the HELP dissemination package, which includes program manuals, business tools, training videotapes or compact discs, and tracking software. Sites receive ongoing support from the HELP Dissemination Team; the HELP Website (http://www.hospitalelderlifeprogram.org), with its program resources and on-line discussion forum; semiannual special interest group meetings; and the annual HELP conference.

Barriers to Dissemination

Two qualitative studies, 129,130 identified common challenges to translating the HELP model into practice. The initial study¹²⁹ examined challenges in initial implementation of the intervention and identified six common challenges: gaining internal support despite differing goals of administration and clinical staff; ensuring effective clinician leadership; integrating with existing geriatric programs (coordination vs competition); balancing program fidelity with local resources (reduce duplication, adaptation); documenting positive outcomes despite limited resources for research; and maintaining momentum despite unrealistic timeframes, limited resources, and staff turnover. A subsequent study¹³⁰ identified three common challenges to sustaining the intervention: presence of clinical leadership, adaptation to local circumstances, and obtaining long-term funding. Obtaining long-term funding represented the ultimate challenge across all sites, and most successful sites demonstrated local benefits and elicited funding through the hospital's operating budget.

Falls

Overview

Falls pose a serious health problem for older persons, occurring in 30% of adults aged 65 and older and 40% of those aged 80 and older.^{98,131} Falls are the leading cause of unintentional injury, which ranks as the sixth leading cause of death in older people.¹³¹ In addition, falls lead to functional decline, hospitalization, institutionalization, and higher healthcare costs.^{98,131} More than 60 intervention trials have been conducted, including multifactorial targeted risk-factor intervention studies,¹³² which have resulted in an approximately 30% relative risk reduction in fall rate. Moreover, fall prevention has been demonstrated to be costeffective, and perhaps cost-saving.¹³² Despite this evidence, fall prevention has been largely neglected in clinical practice. A recent survey of primary care providers documented that only 37% ask patients about falls.¹³³

Dissemination Process

In a local effort to catalyze translation of research into practice, the Connecticut Collaboration for Fall Prevention was implemented to disseminate current evidence throughout the healthcare system in the greater Hartford, Connecticut, area and to embed fall risk evaluation and management into practice by changing knowledge, attitudes, and behavior of healthcare providers.¹³⁴ Healthcare providers targeted for these efforts included emergency departments in seven local hospitals, 212 primary care offices (> 500 physicians), 26 home care agencies (> 200 staff), and 130 rehabilitation centers (> 300 physical therapists). Practice materials on fall risk evaluation and management were developed and circulated, including checklists, manuals, passbooks, and Website (http://www.fallprevention.org/). A variety of professional behavior change strategies^{134,135} were implemented, including general methods to heighten fall awareness and targeted methods to increase fall-related practices. The methods to heighten fall awareness included media presentations (e.g., television, radio, newspaper), monthly newsletters, posters and brochures at clinical and community sites, lectures and in-services, and efforts to publicize the Website. The methods to increase fall-related practices included working groups to facilitate buy-in from local leaders, repeated contacts with providers (e.g., academic detailing¹³⁶), and patient-mediated strategies (e.g., encouraging direct patient requests for fall management).

Barriers to Dissemination

Through interviews with Connecticut Collaboration for Fall Prevention working groups,¹³⁴ barriers to the translation of evidence-based strategies were identified, including knowledge, attitudinal, and organizational barriers. Knowledge barriers included that providers and seniors were not aware of the preventable nature of falls, providers were not familiar with geriatrics or lacked expertise in fall prevention, providers were not aware of the expertise of other providers who would represent appropriate referral resources, and the false perception that Medicare does not cover fall risk evaluation and management. Attitudinal barriers included the lack of importance assigned to falls by providers, providers believing they were already addressing the problem, and patients not requesting attention to their falls. Finally, organizational barriers included the fragmented, uncoordinated nature of the healthcare system; rapid turnover of providers; arcane Medicare reimbursement system for fall-related services; health care focusing on diseases rather than multifactorial geriatric syndromes; competing demands on providers who are bombarded with guidelines; and the lack of a mandate to address falls in clinical practice. Local efforts can go only so far without a national push.

National Efforts to Translate Research into Practice and Policy

Knowing is not enough; we must apply. Willing is not enough; we must do.—Goethe

Table 2 provides examples of national efforts to translate research into practice and policy for geriatric syndromes.¹¹⁷ Examples provided span the areas of educational and clinical efforts, quality improvement approaches, accreditation standards, reimbursement and payment policies, and legislative policies. Although many other initiatives exist, Table 2 provides a few representative examples of areas that are initiated or in process. These examples provide a valuable framework to further address the full scope of common geriatric syndromes.

Medicare reimbursement for common geriatric syndromes remains a critical issue that will need to be addressed to provide appropriate health care for these conditions. Considerable work will be needed to accomplish this goal. Payers are concerned about the potential cost of services, the potential for fraud and abuse, the fact that Medicare typically does not cover coordination of services, and the statutory limitations on coverage (i.e., Medicare usually covers only acute episodes of care). Providers report challenges in providing care to older patients,

Area	Description	Examples		
Educational and clinical efforts	 Clinical practice guidelines and clinical pathways through national organizations 	 Clinical guidelines for falls, delirium, incontinence, pressure ulcers American Geriatrics Society Falls Practice Guidelines 		
	Healthcare coalitions of national and local	· Falls-free coalition (partnering of National		
	organizations Provider education through certifying organizations 	Council on Aging and others) Vulnerable Elderly Practice Improvement Modules through American Board of Internal Medicine 		
	 Web-based educational and clinical programs 	Falls prevention Website, Hospital Elder Life Program Website		
Quality-improvement approaches	 Outreach to seniors Acute Care for Vulnerable Elders quality indicators for geriatric conditions 	 AARP, local and regional efforts Quality indicators for assessing care of vulnerable older people have been developed for 22 key conditions, including dementia, depression, falls, hospital care, incontinence, pressure ulcers. 		
	 Agency for Healthcare Research and Quality National Quality Measures Clearinghouse National Committee for Quality Assurance 	 Quality measures for multiple conditions, including delirium, pressure ulcers, urinary incontinence Posts "report cards" and benchmark quality data for health plans, hospitals, and physicians 		
	 Medicare Payment Advisory Commission—organization that advises congress about Medicare program and policies 	 Reports on Medicare quality of care yearly Falls and wounds as quality-improvement targets for home care 		
	· Patient safety initiatives	· Regional initiatives, local hospitals		
Accreditation standards	 Joint Commission on Accreditation of Healthcare Organizations 	Requires evidence of fall prevention program in many clinical settings		
Reimbursement and	· Establish new diagnosis codes for geriatric	Fall-specific International Classification of		
payment policies	syndromes to facilitate reimbursement · CMS Pay for Performance	Diseases (V-code 15.88) CMS requested American Medical Association Physician Consortium to examine performance improvement measures for falls		
Legislative policies	 National and local legislative efforts to increase patient safety for older persons 	 Fall initiatives involving state legislature,state health departments, social services 		

Table 2. Examples of National Efforts to Translate Research into Practice and Policy

AARP = American Association for Retired Persons; CMS = Centers for Medicare and Medicaid Services.

because Medicare is not accustomed to handling the multiprovider, multisetting model needed to address geriatric syndromes, different types of Medicare contractors may process component services, and variable interpretation of Medicare policies occurs among carriers and intermediaries. These are areas that must be better addressed to provide optimal care for patients with geriatric syndromes.

SUMMARY

Geriatric syndromes represent common, serious conditions for older persons, holding substantial implications for functioning and quality of life. In large part, these conditions are most prevalent in the older population and thus pose distinctive challenges for clinicians caring for this population. The lack of formal criteria to define geriatric syndromes has limited progress in the field. A more-formal recognition of the concepts underlying geriatric syndromes, supported by an improved dialogue between different disciplines, is needed to ensure future progress.

Geriatric syndromes are multifactorial, and shared risk factors—including older age, cognitive impairment, functional impairment, and impaired mobility—were demonstrated across the common geriatric syndromes of pressure ulcers, incontinence, falls, functional decline, and delirium. These findings support the likelihood of shared pathophysiological mechanisms and raise the possibility of a unified approach to prevention of these syndromes.

Studies designed to elucidate the pathophysiology of geriatric syndromes are essential but must embrace the

Table 3. A Call to Action to Enhance Progress in Geriatric Syndromes

Clinical:

- Develop preliminary evidence-based criteria and guidelines for common geriatric syndromes through professional organizations
- · Regularly update criteria and guidelines over time
- Apply criteria and guidelines in clinical practice across disciplines to improve recognition, diagnosis, and management of common geriatric syndromes
- Local demonstration projects for implementation of clinical guidelines and programs to manage common geriatric syndromes Research:
 - Test broader pleiotropic effects of agents (e.g., hormones, statins, antioxidants) or behavioral modifications (e.g., exercise, improved nutrition and weight loss) on relevant outcomes
 - · Explore mechanisms by which such interventions exert effects that are beneficial in specific geriatric syndromes
 - Develop and test unified intervention strategies (based on shared risk factors) across geriatric syndromes and determine the
 effect of these strategies on long-term outcomes
 - Improve the basic pathophysiological understanding of common geriatric syndromes through elucidation of complex mechanistic models that account for multiple pathways and potential synergisms between pathways
- Design more-targeted, more-effective, and safer therapeutic strategies based on these new mechanistic models Policy:
 - Enhance the translation of research into practice at institutional, local, and national levels
 - Work to develop national mandates to overcome barriers to translation, including development of clinical guidelines, quality improvement initiatives, Medicare reimbursement strategies

complex and multifactorial nature of these conditions. Identifying shared common ground or mechanisms will represent a major advance. Simple linear models linking one cause to one effect are not likely to address these conditions suitably. More-complex models, such as concentric models proposed in oncology, should incorporate multiple potential pathways to the outcome as well as the potential for interaction or synergisms between pathways or causes.

Even with substantial progress in clarifying risk factors and intervention strategies for some common geriatric syndromes, such as delirium and falls, these advances have failed to translate widely into clinical practice or policy initiatives. Dissemination programs have been established for delirium and fall prevention, and success and barriers to dissemination have been systematically evaluated. Barriers still exist at patient, provider, and organizational levels.

Table 3 presents a call to action to enhance progress in geriatric syndromes. The challenge of caring for the older population, as exemplified by these common geriatric syndromes, will require paradigm shifts and new approaches to optimize care. These challenges will stretch all of us, as consumers, providers, payers, and policy makers, to improve the healthcare system to better address the needs of the rapidly aging population.

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REFERENCES

- 1. Fried LP, Storer DJ, King DE et al. Diagnosis of illness presentation in the elderly. J Am Geriatr Soc 1991;39:117–123.
- Flacker JM. What is a geriatric syndrome anyway? J Am Geriatr Soc 2003;51:574–576.
- 3. Merriam-Webster Online Dictionary Available at www.m-w.com Accessed on October 24, 2006.
- 4. Stedman's Medical Dictionary. Philadelphia, PA: Lippincott Williams & Wilkins, 2006.
- Olde Rikkert MG, Rigaud AS, van Hoeyweghen RJ et al. Geriatric syndromes: Medical misnomer or progress in geriatrics? Neth J Med 2003;61:83–87.
- Tinetti ME, Inouye SK, Gill TM et al. Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. JAMA 1995;273:1348–1353.
- 7. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56A:M146–M156.

- Ropes MW, Bennett GA, Cobb S et al. Proposed diagnostic criteria for rheumatoid arthritis. Ann Rheum Dis 1957;16:118–125.
- Trimble RB, Townes AS, Robinson H et al. Preliminary criteria for the classification of systemic lupus erythematosus (SLE). Evaluation in early diagnosed SLE and rheumatoid arthritis. Arthritis Rheum 1974;17:184–188.
- McKhann G, Drachman D, Folstein M et al. Clinical Diagnosis of Alzheimer's Disease. Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
- 11. Diagnostic and Statistical Manual of Mental Disorders, 4th Ed. Washington, DC: American Psychiatric Publishing, 2000.
- Ferrucci L, Guralnik JM, Studenski S et al. Designing randomized, controlled trials aimed at preventing or delaying functional decline and disability in frail, older persons: A consensus report. J Am Geriatr Soc 2004;52:625–634.
- Defloor T, Clark M, Witherow A et al. EPUAP statement on prevalence and incidence monitoring of pressure ulcer occurrence. J Tissue Viability 2005;15:20–27.
- Chan EY, Tan SL, Lee CK et al. Prevalence, incidence and predictors of pressure ulcers in a tertiary hospital in Singapore. J Wound Care 2005;14:383–388.
- Chauhan VS, Goel S, Kumar P et al. The prevalence of pressure ulcers in hospitalised patients in a university hospital in India. J Wound Care 2005;14:36–37.
- Gunningberg L. Risk, prevalence and prevention of pressure ulcers in three Swedish healthcare settings. J Wound Care 2004;13:286–290.
- Lindgren M, Unosson M, Krantz AM et al. Pressure ulcer risk factors in patients undergoing surgery. J Adv Nurs 2005;50:605–612.
- Stausberg J, Kroger K, Maier I et al. Pressure ulcers in secondary care. Incidence, prevalence, and relevance. Adv Skin Wound Care 2005;18: 140–145.
- Fisher AR, Wells G, Harrison MB. Factors associated with pressure ulcers in adults in acute care hospitals. Holist Nurs Pract 2004;18:242–253.
- Baumgarten M, Margolis D, Gruber-Baldini AL et al. Pressure ulcers and the transition to long-term care. Adv Skin Wound Care 2003;16: 299–304.
- Dunlop DD, Manheim LM, Sohn MW et al. Incidence of functional limitation in older adults: The impact of gender, race, and chronic conditions. Arch Phys Med Rehabil 2002;83:964–971.
- Margolis DJ, Knauss J, Bilker W et al. Medical conditions as risk factors for pressure ulcers in an outpatient setting. Age Ageing 2003;32:259–264.
- Eachempati SR, Hydo LJ, Barie PS. Factors influencing the development of decubitus ulcers in critically ill surgical patients. Crit Care Med 2001;29:1678–1682.
- Allman RM, Goode PS, Patrick MM et al. Pressure ulcer risk factors among hospitalized patients with activity limitation. JAMA 1995;273:865–870.
- Bergstrom N, Braden B. A prospective study of pressure sore risk among institutionalized elderly. J Am Geriatr Soc 1992;40:747–758.
- Jackson SL, Scholes D, Boyko EJ et al. Urinary incontinence and diabetes in postmenopausal women. Diabetes Care 2005;28:1730–1738.
- Jenkins KR, Fultz NH. Functional impairment as a risk factor for urinary incontinence among older Americans. Neurourol Urodyn 2005;24:51–55.
- Mecocci PSE, von Strauss E, Cherubini A et al. Cognitive impairment is the major risk factor for development of geriatric syndromes during hospitalization: Results from the GIFA study. Dement Geriatr Cogn Disord 2005;20:262–269.
- Nelson RL, Furner SE. Risk factors for the development of fecal and urinary incontinence in Wisconsin nursing home residents. Maturitas 2005;52:26–31.
- Rohr G, Stovring H, Christensen K et al. Characteristics of middle-aged and elderly women with urinary incontinence. Scand J Prim Health Care 2005;23:203–208.
- Saxer S, Halfens RJ, Muller M et al. Risk factors for urinary incontinence in nursing home residents. Swiss Med Wkly 2005;135:495–502.
- Wu J, Baguley IJ. Urinary retention in a general rehabilitation unit: Prevalence, clinical outcome, and the role of screening. Arch Phys Med Rehabil 2005;86:1772–1777.
- Landi F, Cesari M, Russo A et al. Potentially reversible risk factors and urinary incontinence in frail older people living in community. Age Ageing 2003;32:194–199.
- Palmer MH, Baumgarten M, Langenberg P et al. Risk factors for hospitalacquired incontinence in elderly female hip fracture patients. J Gerontol A Biol Sci Med Sci 2002;57A:M672–M677.
- Bergland A, Jarnlo GB, Wyller TB. [Self-reported walking, balance testing and risk of fall among the elderly]. Tidsskr Nor Laegeforen 2006;126: 176–178.
- 36. Arnold CM, Busch AJ, Schachter CL et al. The relationship of intrinsic fall risk factors to a recent history of falling in older women with osteoporosis. J Orthop Sports Phys Ther 2005;35:452–460.

- Fischer ID, Krauss MJ, Dunagan WC et al. Patterns and predictors of inpatient falls and fall-related injuries in a large academic hospital. Infect Control Hosp Epidemiol 2005;26:822–827.
- Gill T, Taylor AW, Pengelly A. A population-based survey of factors relating to the prevalence of falls in older people. Gerontology 2005;51:340–345.
- Horikawa E, Matsui T, Arai H et al. Risk of falls in Alzheimer's disease: A prospective study. Intern Med 2005;44:717–721.
- 40. Kose N, Cuvalci S, Ekici G et al. The risk factors of fall and their correlation with balance, depression, cognitive impairment and mobility skills in elderly nursing home residents. Saudi Med J 2005;26:978–981.
- Kallin K, Gustafson Y, Sandman PO et al. Factors associated with falls among older, cognitively impaired people in geriatric care settings: A populationbased study. Am J Geriatr Psychiatry 2005;13:501–509.
- Murray KJ, Hill K, Phillips B et al. A pilot study of falls risk and vestibular dysfunction in older fallers presenting to hospital emergency departments. Disabil Rehabil 2005;27:499–506.
- Shumway-Cook A, Ciol MA, Gruber W et al. Incidence of and risk factors for falls following hip fracture in community-dwelling older adults. Phys Ther 2005;85:648–655.
- van Doorn C, Gruber-Baldini AL, Zimmerman S et al. Dementia as a risk factor for falls and fall injuries among nursing home residents. J Am Geriatr Soc 2003;51:1213–1218.
- Ishizaki T, Yoshida H, Suzuki T et al. Effects of cognitive function on functional decline among community-dwelling non-disabled older Japanese. Arch Gerontol Geriatr 2006;42:47–58.
- 46. Wu HY, Sahadevan S, Ding YY. Factors associated with functional decline of hospitalised older persons following discharge from an acute geriatric unit. Ann Acad Med Singapore 2006;35:17.
- 47. Cornette P, Swine C, Malhomme B et al. Early evaluation of the risk of functional decline following hospitalization of older patients: Development of a predictive tool. Eur J Public Health 2006;16:203–208.
- Dunlop DD, Semanik P, Song J et al. Risk factors for functional decline in older adults with arthritis. Arthritis Rheum 2005;52:1274–1282.
- Kamper AM, Stott DJ, Hyland M et al. Predictors of functional decline in elderly people with vascular risk factors or disease. Age Ageing 2005;34: 450–455.
- 50. Spiers NA, Matthews RJ, Jagger C et al. Diseases and impairments as risk factors for onset of disability in the older population in England and Wales: Findings from the Medical Research Council Cognitive Function and Ageing Study. J Gerontol A Biol Sci Med Sci 2005;60A:M248–M254.
- Stel VS, Smit JH, Pluijm SM et al. Consequences of falling in older men and women and risk factors for health service use and functional decline. Age Ageing 2004;33:58–65.
- Gill TM, Allore H, Guo Z. Restricted activity and functional decline among community-living older persons. Arch Intern Med 2003;163:1317–1322.
- Wang LBG, van Belle G, Kukull WB et al. Predictors of functional change: A longitudinal study of nondemented people aged 65 and older. J Am Geriatr Soc 2002;50:1525–1534.
- Beland F, Zunzunegui MV. Predictors of functional status in older people living at home. Age Ageing 1999;28:153–159.
- Mor V, Wilcox V, Rakowski W et al. Functional transitions among the elderly: Patterns, predictors, and related hospital use. Am J Public Health 1994;84:1274–1280.
- Wilson K, Broadhurst C, Diver M et al. Plasma insulin growth factor-1 and incident delirium in older people. Int J Geriatr Psychiatry 2005;20:154–159.
- Yamagata K, Onizawa K, Yusa H et al. Risk factors for postoperative delirium in patients undergoing head and neck cancer surgery. Int J Oral Maxillofac Surg 2005;34:33–36.
- Blondell RD, Powell GE, Dodds HN et al. Admission characteristics of trauma patients in whom delirium develops. Am J Surg 2004;187:332–337.
- Kagansky N, Rimon E, Naor S et al. Low incidence of delirium in very old patients after surgery for hip fractures. Am J Geriatr Psychiatry 2004;12:306–314.
- Santos FS, Velasco IT, Fraguas R Jr. Risk factors for delirium in the elderly after coronary artery bypass graft surgery. Int Psychogeriatr 2004;16: 175–193.
- Yoshimura Y, Kubo S, Shirata K et al. Risk factors for postoperative delirium after liver resection for hepatocellular carcinoma. World J Surg 2004;28: 982–986.
- Wang SG, Lee UJ, Goh EK et al. Factors associated with postoperative delirium after major head and neck surgery. Ann Otol Rhinol Laryngol 2004;113:48–51.
- Bohner H, Hummel TC, Habel U et al. Predicting delirium after vascular surgery: A model based on pre- and intraoperative data. Ann Surg 2003;238:149–156.
- Ljubisavljevic V, Kelly B. Risk factors for development of delirium among oncology patients. Gen Hosp Psychiatry 2003;25:345–352.

- 65. Morrison RS, Magaziner J, Gilbert M et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci 2003;58A:M76–M81.
- Fann JR, Roth-Roemer S, Burington BE et al. Delirium in patients undergoing hematopoietic stem cell transplantation. Cancer 2002;95:1971–1981.
- Schneider F, Bohner H, Habel U et al. Risk factors for postoperative delirium in vascular surgery. Gen Hosp Psychiatry 2002;24:28–34.
- Aldemir M, Ozen S, Kara IH et al. Predisposing factors for delirium in the surgical intensive care unit. Crit Care 2001;5:265–270.
- 69. Galanakis P, Bickel H, Gradinger R et al. Acute confusional state in the elderly following hip surgery: Incidence, risk factors and complications. Int J Geriatr Psychiatry 2001;16:349–355.
- Litaker D, Locala J, Franco K et al. Preoperative risk factors for postoperative delirium. Gen Hosp Psychiatry 2001;23:84–89.
- McCusker J, Cole M, Abrahamowicz M et al. Environmental risk factors for delirium in hospitalized older people. J Am Geriatr Soc 2001;49:1327–1334.
- 72. Dubois MJ, Bergeron N, Dumont M et al. Delirium in an intensive care unit: A study of risk factors. Intensive Care Med 2001;27:1297–1304.
- Dai YT, Lou MF, Yip PK et al. Risk factors and incidence of postoperative delirium in elderly Chinese patients. Gerontology 2000;46:28–35.
- 74. Martin NJ, Stones MJ, Young JE et al. Development of delirium: A prospective cohort study in a community hospital. Int Psychogeriatr 2000;12: 117–127.
- Marcantonio ER, Goldman L, Orav EJ et al. The association of intraoperative factors with the development of postoperative delirium. Am J Med 1998;105:380–384.
- Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. JAMA 1996;275:852–857.
- Fisher BW, Flowerdew G. A simple model for predicting postoperative delirium in older patients undergoing elective orthopedic surgery. J Am Geriatr Soc 1995;43:175–178.
- Foy A, O'Connell D, Henry D et al. Benzodiazepine use as a cause of cognitive impairment in elderly hospital inpatients. J Gerontol A Biol Sci Med Sci 1995;50A:M99–M106.
- Marcantonio ER, Goldman L, Mangione CM et al. A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 1994;271: 134–139.
- Pompei P, Foreman M, Rudberg MA et al. Delirium in hospitalized older persons: Outcomes and predictors. J Am Geriatr Soc 1994;42:809–815.
- Inouye SK, Viscoli CM, Horwitz RI et al. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. Ann Intern Med 1993;119:474–481.
- Jitapunkul S, Pillay I, Ebrahim S. Delirium in newly admitted elderly patients: A prospective study. Q J Med 1992;83:307–314.
- Williams-Russo P, Urquhart BL, Sharrock NE et al. Post-operative delirium: Predictors and prognosis in elderly orthopedic patients. J Am Geriatr Soc 1992;40:759–767.
- Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. JAMA 1990;263:1097–1101.
- Rockwood K. Acute confusion in elderly medical patients. J Am Geriatr Soc 1989;37:150–154.
- Rogers MP, Liang MH, Daltroy LH et al. Delirium after elective orthopedic surgery: Risk factors and natural history. Int J Psychiatry Med 1989;19: 109–121.
- Gustafson Y, Berggren D, Brannstrom B et al. Acute confusional states in elderly patients treated for femoral neck fracture. J Am Geriatr Soc 1988;36:525–530.
- Williams MA, Campbell EB, Raynor WJ Jr et al. Predictors of acute confusional states in hospitalized elderly patients. Res Nurs Health 1985;8: 31–40.
- Seymour DG, Henschke PJ, Cape RD et al. Acute confusional states and dementia in the elderly: The role of dehydration/Volume depletion, physical illness and age. Age Ageing 1980;9:137–146.
- 90. Rosenberg LE. The physician-scientist. An essential—and fragile—link in the medical research chain. J Clin Invest 1999;103:1621–1626.
- 91. Goldstein JL, Brown MS. The clinical investigator. Bewitched, bothered, and bewildered—but still beloved. J Clin Invest 1997;99:2803–2812.
- Hamosh A, Scott AF, Amberger JS et al. Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. Nucleic Acids Res 2005;33(Database issue):D514–D517.
- 93. Smith R. In search of 'non-disease'. BMJ 2002;324:883-885.
- 94. Tinetti ME, Fried T. The end of the disease era. Am J Med 2004;116: 179–185.
- 95. Scully JL. What is a disease? EMBO Rep 2004;5:650-653.
- Scriver CR, Sly WS. The Metabolic and Molecular Bases of Inherited Disease, 8th Ed. New York: McGraw – Hill, 2000.

- Decker S, Sausville EA. Preclinical modeling of combination treatments: Fantasy or requirement? Ann N Y Acad Sci 2005;1059:61–69.
- Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988;319: 1701–1707.
- Inouye SK, Bogardus ST Jr, Charpentier PA et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999;340:669–676.
- Allore HG, Tinetti ME, Gill TM et al. Experimental designs for multicomponent interventions among persons with multifactorial geriatric syndromes. Clin Trials 2005;2:13–21.
- 101. Liebman MN. Opening Pandora's box: Clinical data and the study of complex diseases. Sci STKE 2002;2002:PE20.
- Raisz LG. Pathogenesis of osteoporosis. Concepts, conflicts, and prospects. J Clin Invest 2005;115:3318–3325.
- Lorenzo J. Interactions between immune and bone cells: New insights with many remaining questions. J Clin Invest 2000;106:749–752.
- Hock BJ Jr, Lamb BT. Transgenic mouse models of Alzheimer's disease. Trends Genet 2001;17:S7–S12.
- 105. Waltz E. Price of mice to plummet under NIH's new scheme. Nat Med 2005;11:1261.
- Frazier SC. Health outcomes and polypharmacy in elderly individuals: An integrated literature review. J Gerontol Nurs 2005;31:4–11.
- 107. Drake TA, Schadt E, Hannani K et al. Genetic loci determining bone density in mice with diet-induced atherosclerosis. Physiol Genomics 2001;5: 205–215.
- Toye AA, Lippiat JD, Proks P et al. A genetic and physiological study of impaired glucose homeostasis control in C57BL/6J mice. Diabetologia 2005;48:675–686.
- Kuchel GA, DuBose M, Gruman C et al. Aging patterns in mouse strains used in gene deletion studies: Implications for sarcopenic obesity. J Am Geriatr Soc 2006;54:S134–S135.
- 110. Cappola AR, Xue QL, Ferrucci L et al. 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.
- Taylor JA, Kuchel GA. Detrusor underactivity: Clinical features and pathogenesis of an underdiagnosed geriatric condition. J Am Geriatr Soc 2006;54:1920–1932.
- Elbadawi A, Yalla SV, Resnick NM. Structural basis of geriatric voiding dysfunction. II. Aging detrusor: Normal versus impaired contractility. J Urol 1993;150:1657–1667.
- 113. Taylor JA, Zhu Q, Irwin B et al. Null mutation in macrophage migration inhibitory factor (MIF) prevents muscle cell loss and fibrosis in partial bladder outlet obstruction. Am J Physiol Renal Physiol 2006;291: F1343–F1353.
- 114. Kuchel GA, Zhu Q. Role of immune and endocrine factors in detrusor underactivity and urinary retention. J Am Geriatr Soc 2006;54:S13.
- 115. Meyer-Siegler KL, Iczkowski KA, Vera PL. Macrophage migration inhibitory factor is increased in the urine of patients with urinary tract infection: Macrophage migration inhibitory factor-protein complexes in human urine. J Urol 2006;174:1523–1528.
- Gitler MS, Monks A, Sausville EA. Preclinical models for defining efficacy of drug combinations: Mapping the road to the clinic. Mol Cancer Ther 2003;2:929–932.
- 117. Tinetti ME, Gordon C, Lapin P et al. Fall prevention: A case study of the challenges in adopting evidence-based geriatric care practices. Gerontologist 2006;46:717–725.
- 118. Inouye SK. Delirium in older persons. N Engl J Med 2006;354:1157-1165.
- Inouye SK, Foreman MD, Mion LC et al. Nurses' recognition of delirium and its symptoms: Comparison of nurse and researcher ratings. Arch Intern Med 2001;161:2467–2473.
- 120. Inouye SK, Leo-Summers L, Zhang Y et al. A chart-based method for identification of delirium: Validation compared with interviewer ratings using the confusion assessment method. J Am Geriatr Soc 2005;53:312–318.
- 121. Naughton BJ, Saltzman S, Ramadan F et al. A multifactorial intervention to reduce prevalence of delirium and shorten hospital length of stay. J Am Geriatr Soc 2005;53:18–23.
- 122. Tabet N, Hudson S, Sweeney V et al. An educational intervention can prevent delirium on acute medical wards. Age Ageing 2005;34:152–156.
- 123. Milisen K, Foreman MD, Abraham IL et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. J Am Geriatr Soc 2001;49:523–532.
- 124. Marcantonio ER, Flacker JM, Wright RJ et al. Reducing delirium after hip fracture: A randomized trial. J Am Geriatr Soc 2001;49:516–522.
- 125. Inouye SK, Bogardus ST Jr, Baker DI et al. The Hospital Elder Life Program: A model of care to prevent cognitive and functional decline in older hospitalized patients. J Am Geriatr Soc 2000;48:1697–1706.

- 126. Rizzo JA, Bogardus ST Jr, Leo-Summers L et al. Multicomponent targeted intervention to prevent delirium in hospitalized older patients: What is the economic value? Med Care 2001;39:740–752.
- 127. Leslie DL, Zhang Y, Bogardus ST et al. Consequences of preventing delirium in hospitalized older adults on nursing home costs. J Am Geriatr Soc 2005;53:405–409.
- 128. Rubin FH, Williams JT, Lescisin DA et al. Replicating the hospital elder life program in a community hospital and demonstrating effectiveness using quality improvement methodology. J Am Geriatr Soc 2006;54:969–974.
- 129. Bradley EH, Schlesinger M, Webster TR et al. Translating research into clinical practice: making change happen. J Am Geriatr Soc 2004;52:1875–1882.
- 130. Bradley EH, Webster TR, Baker D et al. After adoption: Sustaining the innovation. A case study of disseminating the hospital elder life program. J Am Geriatr Soc 2005;53:1455–1461.
- Tinetti ME, Baker DI, McAvay G et al. A multifactorial intervention to reduce the risk of falling among elderly people living in the community. N Engl J Med 1994;331:821–827.

- 132. Guideline for the prevention of falls in older persons. American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel on Falls Prevention. J Am Geriatr Soc 2001; 49:664–672.
- 133. Wenger WC, Tinetti ME, King MB. Perceptions of physicians on the barriers and facilitators to integrating fall risk evaluation and management into practice. J Gen Intern Med 2006;21:117–122.
- 134. Baker DI, King MB, Fortinsky RH et al. Dissemination of an evidence-based multicomponent fall risk-assessment and—management strategy throughout a geographic area. J Am Geriatr Soc 2005;53:675–680.
- 135. Chou WC, Tinetti ME, King MB et al. Perceptions of physicians on the barriers and facilitators to integrating fall risk evaluation and management into practice. J Gen Intern Med 2006;21:117–122.
- 136. Solomon DH, van Houten GL, Glynn RJ et al. Academic detailing to improve use of broad-spectrum antibiotics at an academic medical center. Arch Intern Med 2001;161:1897–1902.