Ettore "Ted" DeGrazia. *Bronco.* Oil on canvas, 20″ × 20″. Courtesy of DeGrazia Foundation.

*Most older patients derive the same benefits from cancer treatments as younger patients and should not be excluded from treatment based solely on age.*

# Aging, Frailty, and Chemotherapy

*Lodovico Balducci, MD*

**Background:** *In many cases, elderly individuals have not been offered life-saving interventions due to the assumption that these treatments would be too toxic to tolerate.*

**Methods:** *This article offers an overview of the biology of aging, reviews the assessment of an individual's physiologic age, and explores the medical definition of frailty and its implications in cancer treatment.*

**Results:** *The definition of frailty is controversial. Rather than chronologic age, a more accurate assessment relies on individual estimates of life expectancy and functional reserve, including serum levels of interleukin 6 and D-dimer, the levels of a number of inflammatory cytokines, and the circulating level of C-reacting protein. Decision making for optimal cancer treatment in the older-aged patient benefits from a comprehensive geriatric assessment, a functional test, and a laboratory evaluation to determine a patient's life expectancy and functional reserve.*

**Conclusions:** *Most older patients appear to benefit from cancer treatment to an extent comparable to that of younger individuals, and only a minority of these patients should be excluded from treatment due to reduced tolerance.*

*From the Senior Oncology Program at the H. Lee Moffitt Cancer Center & Research Institute, Tampa, Florida.*

*Submitted May 31, 2006; accepted October 2, 2006.*

*Address correspondence to Lodovico Balducci, MD, Senior Adult Oncology Program, H. Lee Moffitt Cancer Center & Research Institute, 12902 Magnolia Drive, Tampa, FL 33612. E-mail: balducci@moffitt.org*

*No significant relationship exists between the author and the companies/organizations whose products or services may be referenced in this article.*

*The editor of Cancer Control, John Horton, MB, ChB, FACP, has nothing to disclose.*

Abbreviations used in this paper: ADLs = activities of daily living, IADLs = instrumental activities of daily living, CGA = comprehensive geriatric assessment, CHS = Cardiovascular Health Study.

## Introduction

The public perception of advanced aging involves the inability to survive alone due to chronic diseases and the combined loss of mobility, sensory functions, and cognition. This image of the older-aged individual, which has been cultivated in literature and figurative arts, has been called frailty, implying that the older person has limited tolerance of even minimal stress.

From a medical standpoint, the classification of aging as frailty has been unfortunate. It has prevented life-saving interventions, including antineoplastic treatment, in older individuals on the assumption that these

**Table 1. — Definitions of Common Terms Used in Geriatric Conditions**

| Term | Definition |
|---|---|
| **Activities of daily living (ADLs)** | Activities necessary for self-care, including transferring, dressing, grooming, feeding, going to the bathroom, and maintaining sphincter continence. |
| **Disability** | A condition in which functional impairment has reached a degree to prevent a specific activity, such as inability to climb stairs due to lower extremities weakness. |
| **Functional dependence** | A condition in which a person is unable to survive without the help of others and may imply dependence in the ADLs or IADLs; though functional dependence is more common in persons with disabilities or handicaps, these are not preconditions to functional dependence and do not necessarily cause functional dependence. |
| **Functional impairment** | Refers to reduced function of a particular organ or system, such as decreased strength of lower extremities. |
| **Geriatric syndromes** | Conditions that, although not unique to aging, become progressively more common with aging, including dementia, severe depression, delirium, falls, spontaneous bone fractures, dizziness, neglect, abuse, and failure to thrive. |
| **Handicap** | A disability that cannot be compensated by environmental changes (eg, the incapacity to climb stairs in the absence of an elevator or a wheelchair ramp to allow a person to reach the upper levels of a building. |
| **Instrumental activities of daily living (IADLs)** | Activities necessary to independent survival: using transportation, shopping, taking medications, managing one's money, providing one's personal nutrition, and using the telephone. |

treatments would be too toxic to tolerate. Contrary to this prediction, the majority of older individuals appear to benefit from cancer treatment to an extent comparable to that of younger individuals,[1] and only a minority of these patients should be excluded from treatment due to reduced tolerance.

Cancer is mostly a disease of the older-aged individual, and it is expected to become even more common with the aging of the population.[2] To ensure optimal treatment of the older cancer patient, it is important not only to dispel the impression that frailty is unavoidable but also to recognize that the older population is highly diverse, which requires individualized assessment and treatment plans. The management of cancer in the older-aged patient should be guided by individual estimates of life expectancy and functional reserve (ie, each patient's ability to benefit from and tolerate treatment) rather than by chronologic age.

This article offers an overview of the biology of aging, reviews the assessment of an individual's physiologic age, and explores the medical definition of frailty and its implications in cancer treatment. Table 1 provides an explanation of terms used in exploring the biology and the assessment of aging.

## Aging: Overview and Biology

The trajectory of aging, which begins in early adulthood, involves progressive decline in the functional reserve of multiple organs and systems (Fig 1). Seemingly, this is due to a combination of factors including predetermined limitation in individual functional reserve, ongoing damage from environmental agents, increased prevalence of chronic diseases, and the emergence of a number of conditions termed *geriatric syndromes*.[2] The loss of functional reserve leads to functional impairment, disability, handicaps, functional dependence, and ultimately death. Loss of functional reserve also increases the susceptibility of older individuals to stress so that acute diseases are more common, more prolonged, more disabling, and more toxic in older individuals. In addition, complications associated with the medical interventions occur more frequently.

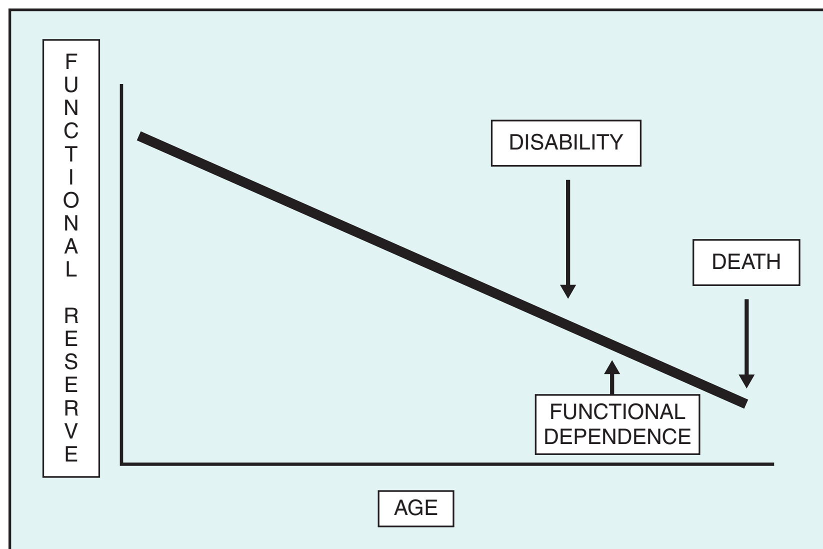


Fig 1. — The trajectory of aging.

### *Questions Regarding the Trajectory of Aging*

*It is universally accepted that death is unavoidable, but can death be delayed?* A current tenet holds that human lifespan is predetermined and cannot be prolonged; animal experiments support this concept. It is probably wise to subscribe to this view, along with recognizing that the management of some genetically determined conditions may prolong individual lifespan. For example, caloric restriction in genetically obese rats has increased the lifespan of these animals with respect to their control littermates fed ad lib, albeit not beyond the lifespan of normal rats.[3] Likewise, it is reasonable to expect that the management of genetic cancers can prolong the survival of affected individuals.

*Can the course of disability and functional dependence be reversed?* While disability and functional dependence can be reversible to some extent, it is generally believed that an individual's functional reserve may become so depleted that no further restoration of a normal function is possible. Efforts to define this "point of no return" have failed so far.[4,5]

*Can disability and functional dependence be delayed?* This is probably the area of geriatrics that has been investigated most intensely. While human lifespan may indeed be predetermined, the onset of disease and disability may be delayed by adopting a healthy lifestyle, by managing chronic conditions such as diabetes and hypertension, and by utilizing preventive measures including early-detection of cancer. The prolongation of the so-called "active life expectancy" of the population suggests that disease and disability may indeed be delayed.[6] Compression of morbidity rather than prolongation of survival may be one of the main goals of cancer management in the older-aged patient.

### *Definition of Aging*

The description of this trajectory results in yet another question — what is aging? Aging has been defined as a loss of "entropy and fractality."[7] Loss of entropy implies a progressive reduction in an individual's functional reserve, whereas loss of fractality implies a progressive reduction in the ability to coordinate different activity and negotiate the environment. The increased incidence of falls, in the absence of specific neurologic or muscular deficits, is an example of loss of fractality with aging. Seemingly, measures of entropy and fractality would provide the most accurate estimate of an individual's real age, but attaining such measures is not possible at present.

Aging is a multifactorial process, but the various pathways that lead to aging merge at a common crossroad. A consistent finding in older individuals is a chronic and progressive inflammation that correlates with functional decline and death as well as a number of geriatric syndromes.[8] Of particular interest:

- For home-dwelling individuals, the serum levels of interleukin 6 (IL-6) and D-dimer, both markers of chronic inflammation, predict functional decline and mortality.[9]
- The levels of a number of inflammatory cytokines have been found to be elevated in common cognitive disorders of aging.[10]
- The circulating level of IL-6 is elevated in most geriatric syndromes and often reflects compromised muscular function.[11]
- The circulating level of C-reacting protein, another inflammatory marker, predicts increased risk of cardiovascular mortality.[12]

The consequences of chronic inflammation are extensive and might include genomic changes that cause cellular loss or that favor carcinogenesis.[13] This article highlights how chronic inflammation can lead to functional decline, reduced immune response, increased vulnerability to diseases, and compromised intellectual function. In part, these effects can be mediated through sarcopenia.[4,5]

The interrelationship of endocrine changes of aging and chronic inflammation is being unraveled. Clearly, chronic inflammation is responsible for increased levels of circulating corticosteroids and increased prevalence of insulin resistance in the older-aged individual. It is less clear how chronic inflammation is related to the production of growth hormones and sexual hormones and to the changes in body compositions occurring with age. The loss of lean body weight and the accumulation of abdominal fat might be caused in part by inflammatory cytokines.[4,14]

The increasing prevalence of mild anemia with aging can also be explained, at least in part, by chronic inflammation. The most common anemia in older individuals is anemia of chronic inflammation that involves a condition of relative erythropoietin deficiency. This is similar to relative insulin deficiency in type 2 diabetes and involves a reduced ability to produce erythropoietin and a reduced response of erythropoietic progenitors to erythropoietin.[15] Another mechanism of anemia in these patients is the inability to mobilize iron from tissue stores. This condition is due to increased circulating levels of hepcidine, a hepatic protein, whose production is also stimulated by IL-6.[16] Anemia of chronic inflammation is reversible with epoetin and its derivatives. Ongoing studies explore the possibility that correction of anemia may reduce the level of chronic inflammation and eventually delay aging.

## Assessment of the Older-Aged Individual

Prevention and treatment of cancer in the elderly are dependent on the answers to three questions: Will the patient die of cancer or with cancer? Will the patient suffer the complications of cancer during his or her lifetime? Is the patient able to tolerate the treatment of cancer?

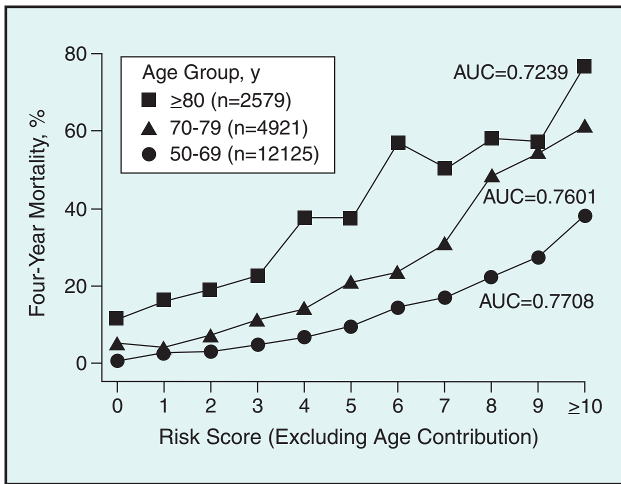


Fig 2. — Four-year mortality by risk score in differing age groups. From Lee SJ, Lindquist K, Segal MR, et al. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA.* 2006;295: 801-808. Copyright © 2006 American Medical Association. Reprinted with permission.

These questions can be answered by a comprehensive geriatric assessment, a functional test, and a laboratory evaluation.

### Comprehensive Geriatric Assessment

This time-honored evaluation of the older-aged individual explores all dimensions of aging including function (expressed as activities of daily living [ADLs] and instrumental activities of daily living [IADLs]), comorbidity (with special attention to cardiovascular diseases, depression, anemia, and other cancers), social support, cognitive status, and presence of geriatric syndromes. The Comprehensive Geriatric Assessment (CGA) has reduced the rate of hospitalization and institutionalization of older individuals and also might have prolonged their survival. In geriatric oncology, the advantages of a CGA are threefold: it identifies reversible conditions that might interfere with the treatment of older patients, it ascertains an estimate of life expectancy and treatment tolerance, and it establishes a common language in the classification of older individuals in alternative to the use of chronologic age.[1] A number of investigators have developed a scoring system based on the CGA that provides an estimate of short- and long-term mortality (Fig 2).[17]

On the other hand, the CGA has a number of limitations: it is cumbersome, time-consuming, and possibly redundant. Also, it has never been standardized. As alternatives to a full geriatric assessment, a number of screening tests have been investigated, including a short questionnaire and proof of physical performance. The Vulnerable Elderly Survey 13 (VES-13) is a 13-item questionnaire that can be completed in a few minutes (Table 2). Patients who screen positive (ie, obtain a score of 3 or higher) should undergo a complete CGA.[3]

### Proof of Physical Function

Several studies have correlated decreased strength of lower extremities with increased risk of disability and reduced survival. One common test is the timed "get up and go" test. The individual being assessed is asked to rise from an armchair, walk 8 feet, and go back to sitting. A score of 1 is given to each of these findings: using the arms to get up, walking with an uncertain gait, and taking more than 10 seconds to complete the activity.[18] The higher the final score, the higher is the risk of developing functional dependence and of dying. In general, patients scoring 1 or higher should undergo a CGA.

The assessment utilized in the Cardiovascular Health Study (CHS), validated in approximately 8,500 individuals followed for an average of 11 years, combines proof of physical function and questionnaires (Table 3).[19] According to the number of abnormalities present, the subjects are divided into three risk groups: mortality, hospitalization, and admission to adult care living facilities. This simple instrument, which can be completed in less than 5 minutes, provides a valuable classification of healthy elderly individuals and can help to identify those who may benefit from interventions of limited efficacy and long-term effect, such as screening for cancer or use of adjuvant chemotherapy. It is also reasonable to utilize the CHS as a screening test to identify patients (pre-frail and frail) who may benefit from a full CGA.

**Table 2. — The Vulnerable Elderly Survey 13 (VES-13)**

**A. Scoring System**

| Element of Assessment | Score |
|---|---|
| **Age** | |
| • 75–84 | 1 |
| • ≥85 | 3 |
| **Self-Reported Health** | |
| • good or excellent | 0 |
| • fair or poor | 1 |
| **ADLs/IADLs** | |
| **Needs helps in:** | |
| • shopping | 1 |
| • managing money | 1 |
| • doing light housework | 1 |
| • transferring | 1 |
| • bathing | 1 |
| **Activities** | |
| **Needs help in:** | |
| • stooping, crouching, or kneeling | 1 |
| • lifting or carrying 10 lbs | 1 |
| • writing of handling small objects | 1 |
| • reaching or extending arm above shoulder | 1 |
| • walking 1/4 mile | 1 |
| • doing heavy housework | 1 |

**B. Vulnerability Scores, Functional Decline, and Survival**

| Score | Risk of Functional Decline or Death |
|---|---|
| 1–2 | 11.8% |
| 3+ | 49.8% |
| 1–3 | 14.8% |
| 4+ | 54.9% |

**Table 3. — Elements of the Cardiovascular Health Study**

- Unintentional weight loss of ≥10 pounds in prior year, by direct measurement of weight.
- Grip strength <20% below standard for body mass index (BMI) measured with Jamar Hand Hydraulic Dynamometer (Lafayette Instruments, Lafayette, Ind).
- Walk time below a cutoff point for sex and height.
- Exhaustion, measured as two statements from the CES-D depression scale.
- Physical activity, measured on the short version of the Minnesota Leisure Time activity (see below). Kcal/week = men: <383; women: <270.

**Subdivision of Patients According to the Results of the Assessment**

| | |
|---|---|
| No abnormalities: | fit |
| 1–2 abnormalities: | pre-frail |
| >2 abnormalities: | frail |

### *Laboratory Evaluation*

As aging involves a progressive and chronic inflammation, it is not surprising that increasing levels of IL-6 and D-dimer were found to predict functional decline and mortality in home-dwelling individuals 70 years of age or greater. The relation of the circulating levels of C-reactive protein on the risk of cardiovascular death is also well known.[9] Inflammatory markers likely have an effect in estimating life expectancy and risk of treatment complications in older cancer patients but this is unproven. At present, the laboratory assessment of aging belongs to the realm of clinical research.

## Aging and Frailty

Fig 3 shows the algorithm utilized at our institution for decisions related to the management of older cancer patients, based on the result of the geriatric assessment. This algorithm is a frame of reference for accommodating the multiple permutations of conditions that may affect older individuals with cancer. As our understanding of aging progresses and our assessment of aging becomes more precise, the algorithm will be modified accordingly.

Patients with dependence in one or more ADLs, with severe comorbidity, and with one or more geriatric syndromes are considered candidates for symptom management only. The underlying assumption is that the functional reserve of these individuals is so limited that they could not tolerate even minimal stress. Originally, we considered these individuals to be frail according to the definition provided by Hamerman[5] who, in attempting a nosology of aging, described frailty as a condition of no return in which the only therapeutic goal should be prevention of further functional deterioration. This definition of frailty is clearly different from that utilized by the CHS, which considers a frail individual an independent person who is more susceptible to stress than a fit one.[19] A recent consensus conference on frailty favored the CHS definition, though an official consensus on the definition of frailty has not yet been reached.

At present, the terms "frail" and "frailty" should be avoided except when used in the context of a CHS assessment. Irrespective of the term, the debate on frailty had the merit to highlight two important theoretical landmarks in the trajectory of aging. The first includes a significant reduction in functional reserve that enhances susceptibility to stress. This condition, which concerns a large part of otherwise healthy and independent individuals over 70 years of age, may be

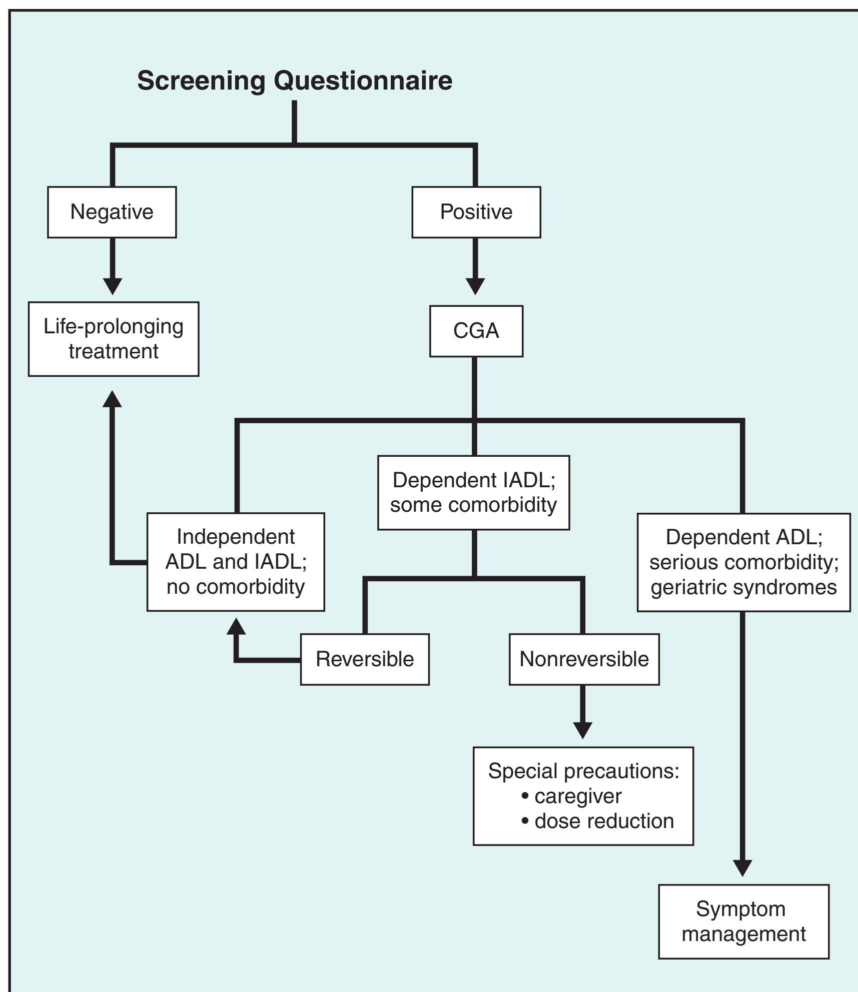


Fig 3. — Algorithm used in decision making of older-aged patients with cancer.

reversible, at least in part, and does not preclude utilization of aggressive life-saving treatment. This condition is called frailty, according to the CHS classification. The second landmark involves exhaustion of the physiologic reserve so that even minimal stress can have catastrophic consequences. This condition is associated with some degree of functional dependence, may be largely irreversible, and allows only symptom management for the preservation of comfort and quality of life. The clinical definition of these landmarks in an important project of geriatric translational research in the direction "from the bedside to the bench."

## Conclusions

Aging involves a progressive loss of entropy and fractality that reduces the tolerance of stress but, in the majority of older individuals, does not prevent effective cancer treatment.

Treatment-related decisions involve the assessment of a patient's life expectancy and functional reserve. In the absence of adequate measurements of entropy and fractality, physiologic age may be assessed with a CGA, with proof of physical function, and with laboratory tests. A number of screening tests limit the CGA to individuals more likely to benefit from it.

The definition of frailty is controversial. Currently, it is prudent to reserve this term to the specific context of the CHS assessment. Ongoing translational research in geriatrics is aimed at identifying the biological and clinical correlates of reduced and exhausted functional reserve.

### References


1. Carreca I, Balducci L, Extermann M. Cancer in the older person. *Cancer Treat Rev*. 2005;31:380-402.
2. Kinney JM. Nutritional frailty, sarcopenia and falls in the elderly. *Curr Opin Nutr Metab Care*. 2004;7:15-20.
3. Masoro EJ. Overview of caloric restriction and aging. *Mech Ageing Dev*. 2005;126:913-922.
4. Zemel MB: The role of dairy foods in weight management. *J Am Coll Nutr*. 2005;24:537S-546S.
5. Hamerman D. Frailty, cancer, cachexia and near death. In: Balducci L, Lyman GH, Ershler WB, et al, eds. *Comprehensive Geriatric Oncology*. 2nd ed. London; New York: Taylor & Francis; 2004.
6. Gill TM, Allore H, Hardy SA, et al. Estimates of active and disabled life expectancy based on different assessment intervals. *J Gerontol A Biol Sci Med Sci*. 2005;60:1013-1016.
7. Lipsitz LA. Physiological complexity, aging, and the path to frailty. *Sci Aging Knowledge Environ*. 2004;pe16.
8. Ferrucci L, Corsi A, Lauretani F, et al. The origins of age-related proinflammatory state. *Blood*. 2005;105:2294-2299. Epub 2004 Nov 30.
9. Cohen HJ, Harris T, Pieper CF. Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. *Am J Med*. 2003;114:180-187.
10. Wilson CJ, Cohen HJ, Pieper CF. Cross-linked fibrin degradation products (D-dimer), plasma cytokines, and cognitive decline in community-dwelling elderly persons. *J Am Geriatr Soc*. 2003;51:1374-1381.
11. Kishimoto T. Interleukin-6: from basic science to medicine — 40 years in immunology. *Annu Rev Immunol*. 2005;23:1-21.
12. Tsimikas S, Willerson JT, Ridker PM. C-reactive protein and other emerging blood biomarkers to optimize risk stratification of vulnerable patients. *J Am Coll Cardiol*. 2006;47(suppl 8):C19-C31.
13. Demierre MF, Higgins PD, Gruber SB, et al. Statins and cancer prevention. *Nat Rev Cancer*. 2005;5:930-942.
14. Duthie ED. Physiology of aging: relevance to symptom perception and treatment tolerance. In: Balducci L, Lyman GH, Ershler WB, et al, eds. *Comprehensive Geriatric Oncology*. 2nd ed. London; New York: Taylor & Francis; 2004.
15. Ershler WB. Pathogenesis of anemia of senescence. In: Balducci L, Ershler WB, de Gaetano G, eds. *Blood Disorders in the Elderly*. Cambridge, Mass: University Press. 2007. In press.
16. Ganz T. Iron metabolism and aging. In: Balducci L, Ershler WB, de Gaetano G, eds. *Blood Disorders in the Elderly*. Cambridge, Mass: University Press; 2007. In press.
17. Lee SJ, Lindquist K, Segal MR, et al. Development and validation of a prognostic index for 4-year mortality in older adults. *JAMA*. 2006;295:801-808.
18. Bergland A, Laake K. Concurrent and predictive validity of "getting up from lying on the floor." *Aging Clin Exp Res*. 2005;17:181-185.
19. Fried LP, Hadley EC, Walston JD, et al. From bedside to bench: research agenda for frailty. *Sci Aging Knowledge Environ*. 2005;pe24.