

Impact of Age, Sex, and Comorbidity on Cancer Therapy and Disease Progression

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ABSTRACT

A theme of personalized medicine was highlighted at the 2009 Annual Meeting of the American Society of Clinical Oncology. To this end, the current review focuses on the impact of host characteristics (such as age, sex, and comorbidity) as they pertain to cancer biology, treatment efficacy, and tolerance. Increasing age is associated with complex changes in physiology, including alterations in renal and hepatic function, and decreased bone marrow reserve. These may in turn result in alterations in pharmacokinetics and toxicity related to many commonly used anticancer agents. Using tools, such as the geriatric assessment, may help to elucidate the physiologic age of the patient as opposed to the chronologic age. Increasing age is paralleled by an increase in comorbidity, and comorbidity may have independent prognostic implications and substantially impact medical decision making in the patient with cancer. Numerous biologic ties between cancer and comorbidity exist, one example being an association of diabetes with an increased risk of disease recurrence and mortality in the setting of colon cancer. Biologic features can also vary by sex; several biomarkers with either prognostic or predictive value (ie, excision-repair cross-complementation group 1 expression, epidermal growth factor receptor mutation, or dihydropyrimidine dehydrogenase polymorphism) may differentiate efficacy or toxicity in males and females. Taken together, age, sex, and comorbidity each encompass a complex array of physiologic and molecular variations that may each aid in personalizing care for the patient with cancer.

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INTRODUCTION

The 2009 Annual Meeting of the American Society of Clinical Oncology stressed personalized medicine, a recognition that each patient is unique in “prognosis, treatment tolerance, supportive care needs, and outcomes.”¹ An essential part of personalized medicine involves understanding how host characteristics (such as age, comorbidity, or sex) affect cancer biology, treatment efficacy, and tolerance. This is particularly important for potentially vulnerable groups, such as older adults or those with comorbid conditions. The main challenge to personalizing and optimizing their care has been their under-representation in clinical trials, despite the fact that approximately 60% of cancer incidence and 70% of cancer mortality occurs in individuals older than 65 years.^{2,3} Furthermore, increasing age is paralleled by an increase in comorbid illnesses.⁴ The presence of comorbidity may preclude participation in certain clinical trials, and among those who do enroll, detailed data regarding comorbid conditions is not routinely captured. Finally, although the significance of sex in the treatment of nonsex-specific malignancies (eg, lung and colorectal cancer) has

long been recognized in seminal studies, preclinical investigations are just now providing insight into the biology underlying these differences.^{5,6}

With the aging of the US and worldwide population and the emergence of personalized medicine, the importance of incorporating patient-related factors into oncology decisions is being recognized. In this article, we review the role of age, sex, and comorbidity in cancer progression and associated therapy, and propose future research that will further aid in the mission of personalized care.

AGE

Cancer is a disease associated with aging—the majority of cancer diagnoses and deaths occur in people older than 65 years—and the United States population is rapidly aging, with a projected doubling in the number of individuals age ≥ 65 from the year 2000 to 2030. On the basis of the aging of the US population and the known association between cancer and aging, a dramatic increase in the number of new cancer diagnoses is projected for the next 20 years (Fig 1). It is anticipated that patients age ≥ 65 will

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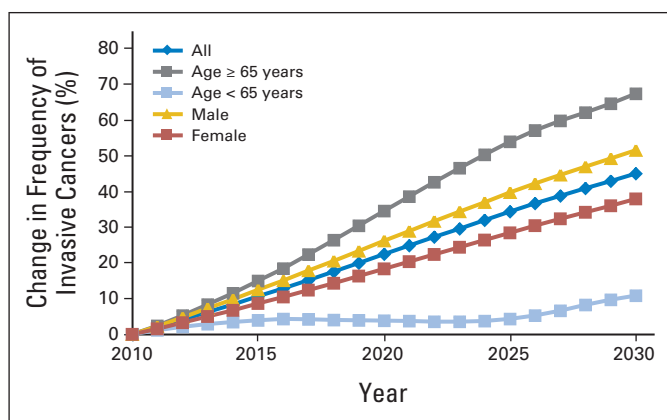


Fig 1. Projected change in frequency of invasive cancers in the United States by age and sex. Nonmelanoma skin cancers were excluded from projections. Data adapted.⁷

account for 70% of all cancer diagnoses by the year 2030.⁷ Numerous explanations have been offered as to the biologic connection between cancer and aging, including extended exposure to carcinogens,⁸ increased DNA instability resulting in a higher mutation potential,⁹ telomere shortening,¹⁰ immune dysregulation,¹¹ and increased susceptibility to oxidative stress.¹² While these explanations for the link between cancer and aging are plausible, they do not pinpoint the reason why one older adult is more susceptible to cancer than another. Furthermore, the association between cancer and aging is complex. Population-based studies demonstrate a steady rise in the probability of developing cancer across the strata of age,¹³ but few studies have examined cancer prevalence and mortality at the extremes of age, and provocative data suggest a potential decrease in cancer prevalence at age ≥ 85 .^{14,15}

Cancer biology may also differ by age at presentation, and understanding the association between the biology of specific cancers and aging can help guide clinical practice. For example, in the setting of acute myeloid leukemia, an increased incidence of unfavorable cyto-

genetics and greater antecedent myelodysplasia is observed among older adults.¹⁶ Similarly, in breast cancer, tumor characteristics vary with age. There is an increase in hormone receptor–positive tumors and a decrease in human epidermal growth factor receptor 2 (HER2) overexpression with increasing age.¹⁷ As HER2 and estrogen receptor (ER) status play a critical role in HER2-directed and endocrine therapies, respectively, understanding age-related variations in expression is critical in determining the particular tumor biology and treatment options. An understanding of tumor biology has already led to some distinct algorithms for treating older individuals.^{18,19}

The aging process is associated with a decrease in physiologic reserve. This decreased reserve can affect tolerance of anticancer therapy secondary to physiologic changes that occur in multiple organ systems. Decreases in renal blood flow and consequent declines in glomerular filtration with age may affect the clearance of cytotoxic agents that are renally excreted, such as cisplatin, carboplatin, etoposide, and methotrexate.^{20–23} A serum creatinine does not accurately reflect renal function in older adults because of the decreasing muscle mass associated with aging. Therefore, a measure of glomerular filtration rate is required to provide a more accurate estimate of renal function with increasing age. Increasing age is also associated with decreased secretion of gastric enzymes and decreased splanchnic blood flow, which may impact the gastrointestinal absorption of orally administered agents, such as capecitabine.^{24,25} Liver mass and cytochrome p450 content appear to decline with increasing age, although the clinical impact of these changes is controversial.^{26,27} Decreased bone marrow reserve with aging may result in increased toxicity with myelosuppressive therapies in older adults.²⁰ As a consequence, National Comprehensive Cancer Network and American Society of Clinical Oncology guidelines note age ≥ 65 as a clinical factor for consideration of primary prophylaxis with WBC growth factors.^{28,29}

Given the complex physiologic changes that accompany aging, several studies have attempted to characterize alterations in pharmacokinetic parameters and resultant toxicities in older adults (Table 1).^{30–41} In turn, these data have prompted efforts to

Table 1. Selected Pharmacokinetic Studies of Single Cytotoxic Agents in Older Adults

Agent	Dosing Regimen	Pharmacokinetic Analysis	Toxicity in Older Adults
Fluorouracil	1,000 mg/m ² IV continuous infusion days 1–5 ³⁰	Clearance: \rightleftharpoons with age; \downarrow in female sex	NR
Capecitabine	2,000 mg oral daily ³¹	Clearance: \rightleftharpoons with age	NR
Docetaxel	40 mg/m ² IV over 2 hours weekly ³²	Clearance: \rightleftharpoons with age	NR
	75 mg/m ² IV over 1 hour every 3 weeks ³³	Clearance: \rightleftharpoons	\uparrow grade 4 neutropenia
Doxorubicin	30–75 mg/m ² IV ³⁴	Clearance: \downarrow with age	NR
Etoposide	50–75 mg/d ³⁵	Clearance: \rightleftharpoons with age	Grade ≥ 3 neutropenia: \uparrow with age
Methotrexate	7.5–15 mg IM weekly ²³	Clearance: \downarrow with age; \uparrow with \uparrow CrCl	NR
Oxaliplatin	130 mg/m ² IV over 2 hours ³⁶	Clearance: \rightleftharpoons with age; \uparrow with \uparrow GFR	Toxicity: \rightleftharpoons with age
Paclitaxel	175 mg/m ² IV over 3 hours every 3 weeks ³⁷	Clearance: \downarrow	Grade ≥ 3 neutropenia: \uparrow with age
	90 mg/m ² IV over 1 hour weekly for 6 weeks followed by a 2-week break ³⁸	Clearance: \downarrow with age	NR
Temozolomide	100–200 mg/m ² /d oral for 5 days every 28 days ³⁹	Clearance: \rightleftharpoons with age	Neutropenia/thrombocytopenia: \uparrow in older females
Vinorelbine	20–30 mg/m ² IV over 10 minutes weekly ⁴⁰	Clearance: \downarrow with age	Anemia/neutropenia: \uparrow with \uparrow AUC
	30 mg/m ² IV days 1 and 8 every 3 weeks ⁴¹	Clearance: \rightleftharpoons	Increased neutropenia

NOTE. Changes observed in older adults reflect either comparison to younger historical cohorts or correlations observed with increasing age.

Abbreviations: IV, intravenous; \rightleftharpoons , no change; \downarrow , decreased; NR, not reported; \uparrow , increased; IM, intramuscular; CrCl, creatinine clearance; GFR, glomerular filtration rate; AUC, area under the curve.

Table 2. Components of the CGA and Selected Examples Indicating the Implications of These Subdomains on Cancer Treatment and Prognosis

CGA Component	Implications for Cancer Treatment and Prognosis: Selected Examples
Functional status	Disability in the IADLs are associated with decreased survival in NSCLC and acute leukemia ^{44,45}
Comorbid (coexisting) medical conditions	Increasing extent of comorbidity has been associated with parallel increases in cancer-specific and all-cause mortality in patients with breast cancer ⁴⁶
Cognition	Presence of dementia may decrease the likelihood of receiving adjuvant systemic therapy in breast and colorectal cancer ^{47,48}
Psychological status	Distress correlates with poorer physical function in patients with solid tumors ⁴⁹
Social functioning and support	An increase in all-cause and cancer-specific mortality has been observed in older women with breast cancer who are socially isolated ⁵⁰
Socioeconomic issues	Older patients with limited finances may forgo purchase of supportive care medications in favor of purchasing anticancer therapy, thereby decreasing their ability to tolerate treatment ⁵¹
Medication review	Studies of older adults with cancer suggest an average of up to 9 medications per patient, with limited efforts to assess for drug-drug interactions with chemotherapy ⁵²
Nutritional status	Weight loss prior to initiation of chemotherapy has been linked to poor outcome in multiple tumor types, including colorectal cancer and NSCLC ^{53,54}

Abbreviations: CGA, Comprehensive Geriatric Assessment; IADL, instrumental activities of daily living; NSCLC, non-small-cell lung cancer.

identify dosing regimens that minimize toxicity but preserve efficacy in older patients.⁴²

Aging is a heterogeneous process. Evaluation tools, such as the comprehensive geriatric assessment, allow for identification of older patients with a higher risk of morbidity and mortality. In these individuals, the risks and benefits of anticancer therapy must be specifically assessed.⁴³ The geriatric assessment includes domains with prognostic relevance that afford insight into the physiologic age of the patient, as opposed to the chronologic age alone (Table 2).⁴⁴⁻⁵⁴ Evaluation with a geriatric assessment is being studied by the Cancer and Leukemia Group B (ClinicalTrials.gov Identifier: NCT00416481).⁵⁵

A clinical phenotype to risk-stratify an older patient population for frailty has been reported in the geriatric literature and is of enormous prognostic value. This phenotype is characterized by five features: self-reported exhaustion, weakness (by grip strength), unintentional weight loss (greater than 10 pounds in the past year), slow walking speed, and low physical activity.⁵⁶ Patients with \geq three or more of these criteria (thereby characterized as frail) have a significantly higher risk of both hospitalization and death as compared with nonfrail individuals. This prognostic phenotype has been validated in several large data sets.^{57,58} Further research is needed to explore the application of these criteria to older adults with cancer.

COMORBIDITY

With increasing age, the number of comorbid illnesses increases. In a study of 7,600 patients older than 55 years with cancer, those age 55 to 64 had an average of 2.9 comorbid conditions compared with patients

age \geq 75, who had an average of 4.2 comorbid conditions.⁵⁹ Comorbidity has important prognostic implications. An observational cohort study including 17,712 patients receiving care for multiple cancer types suggested that the severity of comorbidities affected overall survival (OS) in a dose-dependent fashion, independent of cancer stage.⁴ When formulating a treatment plan, oncologists juxtapose the risk from the malignancy against that of comorbid illness on life expectancy. The effect of treatment in decreasing this risk is also weighed. Utilizing this framework, indolent cancers may be managed more conservatively in the setting of a substantial comorbid disease that is more likely to have an impact on life expectancy. In contrast, more aggressive malignancies warrant cancer therapy if they are more likely to affect life expectancy than the comorbid illness.

In practice, it appears that weighing risks of comorbidity does take place, albeit in the absence of firm guidelines. The presence and extent of comorbidity appears to impact surgical decision making in oncology, such as the use of axillary dissection, radical prostatectomy, and resection for breast, prostate, and lung cancer, respectively.⁶⁰⁻⁶² Similarly, comorbidity appears to affect utilization of chemotherapy across multiple malignancies.⁶³⁻⁶⁵ It is possible that the latter trend reflects studies suggesting greater chemotherapy-related toxicity among patients with comorbidity,^{66,67} although conflicting data does exist.⁶⁸

Specific comorbidities may have a unique bearing on prognosis and treatment outcome. In a series of 5,077 patients treated with neoadjuvant hormone therapy followed by radiation for localized prostate cancer, use of hormone therapy was associated with a higher risk of all-cause mortality in the presence of coronary artery disease, congestive heart failure (CHF), or prior myocardial infarction (26.3% v 11.2%; $P = .04$).⁶⁹ In contrast, no increased risk of mortality was observed in men without comorbidity or with only one coronary artery disease risk factor. Other studies have investigated the role of diabetes in the progression of malignancy. Subset analyses of Intergroup-0089 (INT-0089), a randomized trial comparing four fluorouracil-based adjuvant therapy regimens in patients with stage II and III colon cancer, supported several smaller studies that identified a higher rate of overall mortality in patients with colon cancer who also had diabetes.⁷⁰⁻⁷² Molecular rationale for this phenomenon may be linked to elevated serum levels of insulin, which accelerates proliferation of colorectal cell lines.⁷³ Providing clinical validation for this theory, a study of surgically resected patients with colorectal cancer reported that higher levels of C peptide and low levels of insulin-like growth factor binding protein-1 were associated with increased mortality.⁷⁴ Similar findings have been noted in patients with breast cancer, where elevated fasting insulin levels have been associated with an increased risk of distant recurrence and mortality in early-stage disease.⁷⁵ These studies have led to the development of clinical trials evaluating whether modulating the insulin axis would affect cancer outcomes. A provocative study assessing patients from the M. D. Anderson Cancer Registry identified a higher rate of pathologic complete response with neoadjuvant chemotherapy among diabetic patients taking metformin as compared with nondiabetic patients.⁷⁶ These and other supporting data have led to the development of a phase III intergroup trial (National Cancer Institute of Canada MA.32) examining the effect of metformin as adjuvant therapy for breast cancer.⁷⁷ The evolving understanding of the relationship between breast cancer and diabetes, ultimately leading to a potential

therapeutic intervention, underscores the importance of understanding the link between comorbidity and cancer.

It is increasingly recognized that comorbidity may also have a substantial impact on treatment tolerance. In the setting of advanced lung cancer, a randomized trial comparing vinorelbine alone or in combination with gemcitabine demonstrated a higher rate of treatment discontinuation among patients with a Charlson comorbidity index (CCI) score of higher than 2.⁷⁸ Supporting this finding, data from a series of patients with breast cancer receiving dose-dense adjuvant chemotherapy identified an association between comorbidity (defined as a CCI ≥ 1) and grade 3/4 toxicity.⁷⁹ Certain comorbidities may have an impact on tolerance for specific therapies as well. For instance, early observations with paclitaxel therapy suggested an increased risk for severe neuropathy in patients with a concomitant diagnosis of diabetes.⁸⁰ Similarly, the risk of cardiac toxicity with the HER2-directed monoclonal antibody trastuzumab is higher in patients with pre-existing hypertension.^{81,82}

Of note, an effort should be made to distinguish comorbidity from treatment-related toxicity, as these may have different prognostic implications. As one example, the vascular endothelial growth factor targeting antibody bevacizumab has been noted to cause hypertension in clinical application across malignancies.⁸³⁻⁸⁵ Subset analyses from pivotal trials of bevacizumab in lung and breast cancer have associated the development of hypertension with extended OS.^{86,87} These results have led some investigators to question whether hypertension should be considered a dose-limiting toxicity.⁸⁸

SEX

The approach to diseases such as prostate and breast cancer has been guided by an understanding of distinct hormonal axes in males and females, respectively. In other malignancies more evenly distributed between the sexes, key differences in biology between men and women are increasingly recognized. These differences often lead to variations in therapeutic response, toxicity, and clinical outcome. For instance, in the early 1990s, female sex was identified as an independent predictor of survival in patients with lung cancer.⁸⁹ It has been surmised that molecular variations may account for this difference. As one example, excision-repair cross-complementation group 1 (ERCC1), a DNA repair protein, has previously been validated as a predictor of survival with platinum-based therapy for non-small-cell lung cancer (NSCLC) in the adjuvant and metastatic setting.⁹⁰⁻⁹² In patients with inoperable NSCLC, receiving first-line therapy with cisplatin and gemcitabine and lack of ERCC1 expression characterized a subset of males with poorer OS (7.9 v 11.8 months; $P = .005$).⁹³ In contrast, OS was no different in females with ERCC1-negative or -positive tumors (12.6 v 12.3 months; $P = .70$). Other molecular aberrations may predict differences in response to novel targeted therapies for NSCLC. A phase III trial of the epidermal growth factor receptor (EGFR) inhibitor erlotinib demonstrated improved survival with the agent (compared with placebo) after first- or second-line therapy.⁹⁴ The study further identified enhanced response rates among females and those with EGFR mutation, a finding supported by several other investigations of erlotinib and the related EGFR inhibitor gefitinib.⁹⁴⁻⁹⁸ Higher rates of EGFR mutation have been found in female patients with NSCLC, perhaps accounting in part for the discrepancy in response rates by sex.⁹⁹

Aside from differences in clinical outcome, men and women may differ in the extent to which they experience toxicity from chemotherapy and biologics. A meta-analysis including 1,006 patients with small-cell lung cancer enrolled in one of four National Cancer Institute of Canada chemotherapy protocols demonstrated more frequent hematologic toxicity (grade 3 or 4) and gastrointestinal toxicity (all grades) in women.¹⁰⁰ Interestingly, females were noted to have improved response rates and OS with the regimens that included etoposide and cisplatin and cyclophosphamide, doxorubicin, and vincristine.

Other studies have suggested that molecular variations may account for differences in toxicity by sex—as one example, polymorphisms in dihydropyrimidine dehydrogenase (*DYPD*) have been noted to predict grade 3 and 4 toxicity from fluorouracil-based therapy for colorectal cancer.¹⁰¹ In the same study, a strong association between sex and *DYPD* polymorphism has been observed—while the odds ratio for toxicity in males with *DYPD* polymorphism is 41.3 (95% CI, 9.2 to 190; $P < .001$), the odds ratio for females with the same polymorphism is 1.33 (95% CI, 0.34 to 5.2; $P = .68$). Whereas this study and others have reported a higher rate of toxicity from fluorouracil-based therapy in women (possibly due to increased *DYPD* deficiency),^{102,103} it appears that this finding was independent on *DYPD* genotype. Globally, variations in hepatic p-glycoprotein levels (approximately two-fold higher in males than females) may prolong the half-life of various agents, including vinca alkaloids, doxorubicin, etoposide, and docetaxel.^{104,105} Decreased levels of this drug efflux protein may lead to accumulation of these agents and consequent toxicity.^{106,107}

Mounting evidence suggests that the hormonal axes differentiating men and women could play a role in the pathogenesis and progression of other malignancies outside of male genitourinary and gynecologic cancers. For example, in a series of 228 patients with operable NSCLC, 106 patients (46.5%) demonstrated progesterone receptor (PR) immunoreactivity.¹⁰⁸ Positive staining for PR was associated with lower TNM stage, increased histologic differentiation, and improved OS. Accompanying in vitro studies suggested an inhibitory effect of progesterone in PR-positive NSCLC cell lines, suggesting a potential therapeutic role for hormone therapy. ER may also play a prognostic role in NSCLC. Specimens from a series of 447 patients with lung adenocarcinoma revealed nuclear expression of ER- β in 217 patients (48.5%).¹⁰⁹ Interestingly, the prognostic role of nuclear ER- β was limited to patients with concomitant EGFR mutation, where expression was related to improved disease-free survival.

LINKING AGE, SEX, AND COMORBIDITY

While the data presented thus far provide evidence for the separate predictive capabilities of age, sex, and comorbidity in patients with cancer, there are many associations among these variables. Currently, several other prognostic indices for older adults incorporate age, sex, and/or comorbidity (Table 3).¹¹⁰⁻¹¹³ For example, Lee et al¹¹² developed a model for 4-year mortality in the general geriatric population which includes age, sex, and comorbidity. Other indices include two of the three variables. For instance, the CCI has been applied to determine the risk of mortality associated with increasing levels of comorbidity (including cancer).¹¹⁴ In external

Table 3. Indices Utilizing Age, Sex, and/or Comorbidity to Predict Risk of Mortality for Older Adults

Reference	No.	Domains Incorporated			Predictive Capability
		Age	Sex	Comorbidity	
Charlson et al ¹¹⁰	218	Yes	No	Yes	5-year mortality
Inouye et al ¹¹¹	318	No	No	Yes	2-year mortality
Lee et al ¹¹²	8,009	Yes	Yes	Yes	4-year mortality
Walter et al ¹¹³	1,427	No	Yes	Yes	1-year mortality

validation of the CCI, it was demonstrated that consideration of age as an adjunct to the CCI could improve the predictive capability of the tool.¹¹⁰ Studies in the geriatric oncology population have also demonstrated the importance of these variables. In the setting of colorectal carcinoma, a model developed through a Surveillance, Epidemiology, and End Results registry review utilized the three variables in addition to disease stage to predict early mortality.⁷² Other studies demonstrate a link between comorbidity and clinical outcome among older adults with cancer. A Surveillance, Epidemiology, and End Results-Medicare analysis of 29,733 patients with stage I to III colorectal cancer age 67 or older suggested that a substantial proportion of deaths in this population could be attributed to concomitant diagnoses of diabetes mellitus, chronic obstructive pulmonary disease, and/or CHF.¹¹⁵ In the setting of hematologic malignancies, a series of 1,708 patients age 66 or older with myelodysplastic syndrome identified the CCI as a significant predictor of mortality; specifically, patients with CHF and/or chronic obstructive pulmonary disease had significantly shorter survival.¹¹⁶ The link between age, comorbidity, and clinical outcome has been made in the setting of multiple other malignancies, including prostate, lung, and ovarian cancer.¹¹⁷⁻¹¹⁹

More specific molecular variations may differ with age and sex. The tumor suppressor *p16^{INK4a}* has been noted to be a potential marker of physiologic age because with aging, *p16^{INK4a}* expression increases in the tissues of both humans and rodents.¹²⁰ Aberrant methylation of the tumor suppressor gene *p16^{INK4a}* is seen primarily in females and patients of advanced age, a finding seen in both colorectal cancer and hepatocellular carcinoma.^{121,122} In colorectal cancer, hypermethylation of *p16^{INK4a}* appeared to occur in poorly differentiated tumors. As another example of age and sex associations with a distinct genotype, the SNP309 polymorphism in *MDM2* (a negative regulator of p53), which has been associated with melanoma in women younger than 50 years.¹²³ As similar molecular markers are identified in the future, therapeutic strategies may emerge based on specific demographic criteria.

SUMMARY

Reflecting on the theme of personalized medicine, the data described here provide a framework in which to consider age, sex, and comor-

bidity in cancer biology and treatment. Each element portends distinct prognostic value, and is associated with both shared and unique molecular attributes.

Despite the progress being made in understanding the implications of these variables, challenges remain. While age follows a continuum and sex can be represented as a dichotomous variable, comorbidity is more challenging to characterize. In response, the National Institute on Aging Geriatrics and Gerontology program has assembled a taskforce to specifically address the construction of comorbidity measures, proposing standardized schema such as the staging algorithms employed in cancer.¹²⁴

A separate but important barrier related to older adults and patients with comorbidities is their under-representation in clinical trials.² In addition to inclusion in standard protocols, trials that address age-specific needs in older adults may also yield vital insights.¹²⁵ To promote enrollment of older adults in trials, it may be necessary to relax the eligibility criteria by focusing on developing therapeutics in patients with comorbid illnesses, with particular attention to the association between comorbidity and treatment tolerance.¹²⁶

Given the advancing age of US society and the world at large, clinical trials focused on optimizing cancer therapeutics for both fit and frail older adults are urgently needed.

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