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Commentary

COMMENTARY

Measuring Aging and Identifying Aging Phenotypes in Cancer Survivors

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Abstract

Observational data have shown that some cancer survivors develop chronic conditions like frailty, sarcopenia, cardiac dysfunction, and mild cognitive impairment earlier and/or at a greater burden than similarly aged individuals never diagnosed with cancer or exposed to systemic or targeted cancer therapies. In aggregate, cancer- and treatment-related physical, cognitive, and psychosocial late- and long-term morbidities experienced by cancer survivors are hypothesized to represent accelerated or accentuated aging trajectories. However, conceptual, measurement, and methodological challenges have constrained efforts to identify, predict, and mitigate aging-related consequences of cancer and cancer treatment. In July 2018, the National Cancer Institute convened basic, clinical, and translational science experts for a think tank titled "Measuring Aging and Identifying Aging Phenotypes in Cancer Survivors." Through the resulting deliberations, several research and resource needs were identified, including longitudinal studies to examine aging trajectories that include detailed data from before, during, and after cancer treatment; mechanistic studies to elucidate the pathways that lead to the emergence of aging phenotypes in cancer survivors; long-term clinical surveillance to monitor survivors for late-emerging effects; and tools to integrate multiple data sources to inform understanding of how cancer and its therapies contribute to the aging process. Addressing these needs will help expand the evidence base and inform strategies to optimize healthy aging of cancer survivors.

There is a synergistic, bidirectional relationship between cancer and aging. Age is a risk factor for adult cancers (1,2), and emerging evidence suggests that cancer and its treatments might accelerate aging (3–5). The aging process is often described as a gradual accumulation of cellular and molecular damage leading to system dysregulation, which may enable injured cells to become carcinogenic (6,7). Cancer therapies also deliver genotoxic and cytotoxic insults, often causing deleterious changes (3,4,6–8). Thus, cancer, cancer treatments, and aging share at least one common underlying mechanism—the accumulation of damage (7).

During "normal" aging, the buildup of damage across the life span eventually exceeds the body's capacity to self-repair (7,9), producing changes in body composition, energy balance, homeostasis, and neuronal function (10). Various combinations of deficits across these domains can result in a range of

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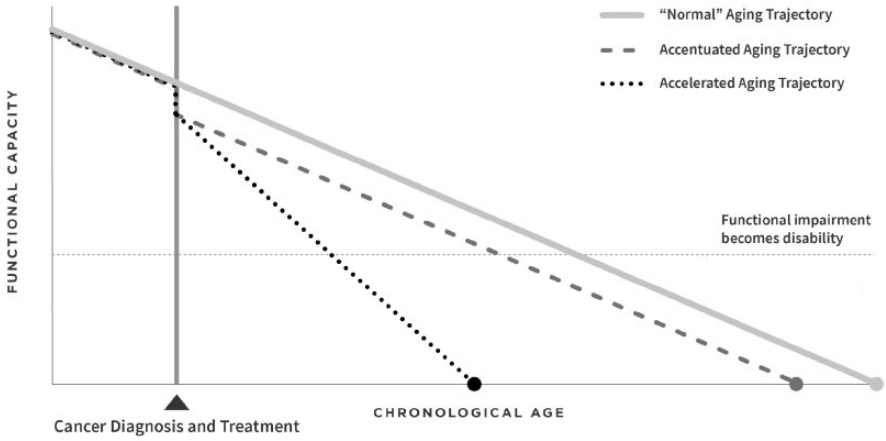

Figure 1. Hypothesized trajectories of aging-related consequences of cancer and cancer treatment.

common aging-related conditions, including frailty, sarcopenia, cardiovascular disease, and cognitive and functional decline (11).

In some individuals, cancer and its treatments are hypothesized to create sufficient damage to accelerate or accentuate the rate of aging compared with that expected in the absence of cancer (3–5). It is unknown if cancer and its treatments cause multiple "hits" to biological systems leading to a paralleled "normal" aging trajectory with weakened reserve (Phase Shift or Accentuated Aging Hypothesis) or an altered aging trajectory with quicker progression to functional decline (Accelerated Aging Hypothesis) (Figure 1) (12). To assert that cancer and its treatments accelerate or accentuate aging, the following criteria outlined by Margolick and Ferrucci must be met: "1) the anatomic and functional manifestations seen must be the same as those seen in usual aging; 2) the mechanisms underlying these manifestations must be the same as in aging, and 3) manifestations and mechanisms should both be detected at a younger age than usual." (10) Evidence from preclinical models shows that radiation (13–15) and genotoxic and cytotoxic anticancer therapies, such as cisplatin, doxorubicin, paclitaxel, and temozolomide, cause physiological changes consistent with several molecular and cellular hallmarks of aging (7), including increased inflammation (15,16), expanded senescent cell burden (17–21), decreased stem cells (15), and persistent DNA damage and decreased telomere length (8,22–25). Compelling evidence from long-term follow-up studies of pediatric and adolescent and young adult cancer survivors suggests that cancer treatment contributes to the onset of aging-related conditions, such as incident comorbidities, functional loss, frailty, and cognitive decline, decades earlier in life than expected (3,5,26–32). Furthermore, observational studies have shown that survivors of adult-onset cancers have a higher burden of mobility limitations (33), comorbid conditions (34), and pain (34), and a greater risk of functional and cognitive impairments compared with healthy, age-matched controls (35–38).

Collectively, these findings suggest that cancer and its therapies may produce unintended aging-related consequences. However, conceptual, measurement, and methodological challenges have constrained efforts to identify, predict, and mitigate the aging-related consequences of cancer and cancer treatment. To address these constraints, in July 2018, the National Cancer Institute (NCI) convened a think tank titled "Measuring Aging and Identifying Aging Phenotypes in Cancer Survivors." Think tank presentations and discussions were guided by critical questions generated by a planning committee of federal government (ie, NCI and National Institute on Aging) and academic representatives. Arti Hurria, MD, of the City of Hope, and Jennifer Schrack, PhD, of the Johns Hopkins Bloomberg School of Public Health, served as meeting chairs. The meeting's scientific discourse was enriched by the representation of diverse disciplinary perspectives including clinical oncology, cancer biology, aging biology, gerontology and geriatrics, psychology, epidemiology, physical therapy, cognitive science, and systems biology. This report synthesizes expert-informed deliberations primed by the think tank and highlights opportunities to expand the evidence base for aging-related consequences of cancer and cancer treatment.

Conceptual and Measurement Considerations

Chronological age, or time since birth, is a proxy for underlying physiological processes that change or accumulate over time (39). It is positively associated with mortality, cancer, and other morbidities, but it is not an etiologic factor and does not fully explain the phenotypic and functional variability observed as individuals age (40–42). For example, one 75-year-old individual might be frail and use a wheelchair, whereas another might be fit and run marathons, thus displaying quite different functional ages or abilities to perform certain activities. Biological age, as defined by Baker and Sprott, refers to the "biological parameter[s] of an organism that either alone or in some multivariate composite will, in the absence of disease, better predict functional capability at some late age than will chronological age." (42) Ideally, biological and functional age should be strongly correlated, because as physiologic damage accumulates and repair capacity becomes compromised, functional decline eventually ensues (43).

The ability to advance knowledge of the short- and long-term effects of cancer and its treatment on aging trajectories has been constrained by a paucity of agreed-on measures to assess aging processes and aging phenotypes in cancer survivors (10,43). Think tank deliberations centered on clinical and biological measures that capture heterogeneity in aging processes, are aligned with the hallmarks of aging, (7) and have established relationships with cancer, cancer treatments, mortality, or other aging-related endpoints. Table 1 presents measures of aging to consider in studies of aging-related consequences of

Table 1. Measures to consider including in research studies of aging-related consequences of cancer and cancer treatment*

Measures	References
Gait speed	Studenski et al., 2011 (44) Studenski et al., 2003 (45) Cooper et al., 2010 (46) Abellan van Kan et al., 2009 (47)
Timed Up and Go	Podsiadlo et al., 1991 (48)
Grip strength	Cooper et al., 2010 (46)
Fried (CHS) Frailty Phenotype	Fried et al., 2001 (49) De Vries et al., 2011 (50)
Deficit Accumulation Index/Frailty Index	Mitnitski et al., 2001 (51) De Vries et al., 2011 (50)
Clinical geriatric assessment	Hurria et al., 2011 (52) Hurria et al., 2005 (53) Hurria et al., 2016 (54) Extermann et al., 2012 (55) Avelino-Silva et al., 2014 (56) Jonna et al., 2016 (57)
Self-rated health	Sargent-Cox et al., 2012 (58) Levy et al., 2002 (59) Demakakos et al., 2018 (60) Kotter-Grühn et al., 2009 (61)
Cognitive assessments	Lai et al., 2014 (62)
Hopkins Verbal Learning Test-Revised	Wefel et al., 2011 (63)
Controlled Oral Word Association Test	Wefel et al., 2011 (63)
The Trail Making Test	Wefel et al., 2011 (63)
Functional Assessment of Cancer Therapy–Cognitive (FACT-Cog)	Cella et al., 1993 (64)
PROMIS Cognitive Function and Cognitive Function–Abilities	Fries et al., 2005 (65) Lai et al., 2014 (62)
Fatigability	Simonsick et al., 2014 (66) Simonsick et al., 2016 (67) Gresham et al., 2018 (36)
APOE4	Deelan et al., 2011 (68)
31p recovery time	Hill et al., 2014 (69) Mulder et al., 2009 (70) Choi et al., 2016 (71) Zane et al., 2017 (72)
P16INK4a	He et al., 2017 (73)
Hannum's clock (DNAm)	Hannum et al., 2013 (74)
Horvath's clock (DNAm)	Booth et al., 2016 (75) Horvath et al., 2018 (76) Horvath 2013 (77)
PhenoAge (DNAm)	Levine et al., 2018 (78) Liu et al., 2018 (79)

*This table provides a list of measures to capture heterogeneity in aging processes and aging-related functional outcomes. Although some measures can be used independently, others, such as the geriatric assessment, require compilation into a composite variable. 31p = 31Phosphocreatine; *APOE4* = apolipoprotein E4; CHS = Cardiovascular Health Study; DNAm = DNA methylation.

cancer and cancer treatment. Box 1 summarizes additional conceptual and measurement considerations discussed during the think tank.

Clinical Measures

Although a variety of clinical measures of aging exist, think tank deliberations focused on measures of functional status, deficit accumulation, and cognitive function because of their previously reported associations with mortality and/or likely impact on aging-related outcomes in older adults and cancer survivors (43).

Box 1. Conceptual, measurement, and methodological considerations for research studies on aging-related consequences of cancer and cancer treatment

Conceptual Considerations

- Consider aging from a life-course perspective with an assessment of aging trajectories across all age groups.
- Engage systems biology to better understand aging processes and trajectories from a cumulative deficit perspective.

Measurement Considerations

- Use clinically feasible, validated measures of physical and cognitive function that improve sensitivity, reduce participant burden, and are robust to age, ceiling, and floor effects.
- Use at least one objective measure of functional status in clinical research studies, such as gait speed or grip strength, at a minimum.

Methodological Considerations

- Leverage existing longitudinal measures and cohort studies, preclinical models, and pooled datasets or consortia, and conduct an initial study of common cancers (eg, breast and prostate) to enroll a large enough sample with variability by cancer type, therapy type, and past exposures to discern the role of cancer and its treatment on aging trajectories.
- Increase the number of older adult cancer patients with comorbid conditions in clinical trials.
- Incorporate adaptive designs to achieve a suitable sample size and adequate precision in the outcome measure.
- Identify the most important predictors and outcomes to ensure enough participant variability and statistical power, given available financial resources.
- Direct attention to survival bias in aging research (cancer survivors with the highest accumulation of deficits will die earlier and may not be captured in research studies).

Functional Status

Functional status can be measured subjectively and objectively. Commonly used subjective measures of functional status in aging studies include the Activities of Daily Living and Instrumental Activities of Daily Living. In oncology settings, the Eastern Cooperative Oncology Group and Karnofsky performance status scales are frequently used and are predictive of cancer survival (80–82). Objective measures of functional status include grip strength, gait speed, chair stands, and balance. Among these, gait speed and grip strength are predictive of adverse health outcomes, including mortality, and are feasible to measure in a clinical setting (44,45,83).

Many measures of physical function have a detection ceiling or floor, which challenges the ability to derive an accurate assessment of functional outcomes among cancer survivors with high- or low-performance status (84). Ceiling effects often occur in younger, healthier cancer survivors, whereas floor effects

typically are observed in the oldest, nonambulatory patients. This challenge could be addressed with sequential testing, in which all participants are first tested using a validated, basic measure of function (eg, walk test). If an individual performs at the ceiling or floor of the initial test, then additional validated assessments can be used to discriminate functional limits and abilities. It should be noted that the inability to perform the functional test itself is a valuable indicator of health.

Deficit Accumulation

Much of the think tank discussion focused on measures of deficit accumulation (eg, frailty and the geriatric assessment [GA]) to comprehensively evaluate aging-related outcomes in adult cancer survivors, because it reflects cumulative multisystem deterioration and nonspecific vulnerability to adverse outcomes (43). There are several measures of frailty (49–51,85–87), including the use of clinical judgment (87), rule-based approaches defined by the presence of symptoms (eg, Fried Frailty Phenotype) (49), and calculating the number of deficits (eg, the deficit accumulation/frailty index or GA) (51). The Fried Frailty Phenotype, deficit accumulation/frailty index, and GA predict functional decline, hospitalization rates, and mortality (27,49,50,86,88–90) (although the GA-mortality association in cancer survivors is less studied) (91–94). The GA assesses multiple domains of illness and health, including functional status, comorbidity, nutritional status, cognition, social support, polypharmacy, and psychological state (eg, depression, anxiety, and distress) (95–97), and is predictive of chemotherapy toxicity and survival in geriatric oncology samples (43,97,98). Recently, the American Society of Clinical Oncology recommended the GA for cancer patients 65 years and older receiving chemotherapy (95).

In the cancer context, the measurement of frailty and other treatment-related outcomes should be modified when necessary to consider domains relevant to pediatric, adolescent and young adult, and midlife adult cancer survivors. For example, assessing comorbidities at the point of diagnosis may be less relevant to the prediction of treatment-associated frailty risk among childhood and adolescent and young adult cancer survivors. Future studies may consider reconceptualizing frailty on a continuum ranging from "fit" to "frail" because intrinsic capacity starts to decline early in adulthood and eventually contributes to the development of frailty (99). The concept of physical and psychological resilience can be studied as a key predictor, modifier, or outcome to inform aging processes in cancer survivors. Resilience may also explain why some older cancer survivors return to relatively normal levels of physical function after receiving treatment, whereas others experience lower or more rapidly decreasing levels (12).

Cognitive Function

Evidence suggests that cancer and its treatments can have short- and long-term impacts on cognitive function in a subset of cancer survivors (38,100–102). Although most research has been conducted in breast cancer patients treated with chemotherapy with or without hormonal treatment, similar results are emerging across other cancer diagnoses (eg, colon, prostate, lymphoma, and testicular) and treatment modalities (cranial and non-central nervous system radiation, endocrine, and hormone ablation therapies) (101). Cognitive domains affected by a variety of cancer treatment modalities include memory (ie, working and recognition), processing speed, attention, and executive function (101). To facilitate comparison across studies, the International Cognition and Cancer Task Force recommends use of the Hopkins Verbal Learning Test-Revised (learning and memory), the Controlled Oral Word Association Test (verbal fluency and executive function), and the Trail Making Test (executive function) to assess cancer-related cognitive impairment (CRCI) (63). Think tank participants reflected on using self-reported measures (eg, Functional Assessment of Cancer Therapy–Cognitive and the Patient-Reported Outcomes Measurement Information System Cognitive Function and Cognitive Function–Abilities) (64,65) as well as the utility of refining neurocognitive measures to reduce assessment burden and improve feasibility in clinical and research settings while preserving sensitivity to detect small changes in function. Think tank participants discussed the potential value of leveraging cognitive neuroscience paradigms to improve measurement sensitivity and specificity of the cognitive processes and domains affected by cancer and cancer treatment exposures (103).

Think tank participants noted that neuroimaging techniques to assess changes in brain structure and function are promising and feasible to conduct in research settings. Moreover, blood, plasma, or other fluid biomarkers, like cerebral spinal fluid analytes collected clinically for central nervous system lymphoma, might be used to elucidate mechanisms of CRCI (104).

Additional inquiry is needed to clarify why certain areas of the brain are more vulnerable to cancer treatments. There are emerging and consistent observations that individuals with the apolipoprotein E4 (*APOE4*) gene polymorphism, the strongest genetic risk factor for Alzheimer disease, are more susceptible to cancer-related cognitive decline than those with other *APOE* genotypes (100,102,105). These observations suggest that gene-treatment interactions may accelerate brain aging or affect intermediate aging processes that in turn influence cognition. Cross-disciplinary studies both of cancer survivors and non-cancer populations with cognitive decline or Alzheimer disease could be leveraged to understand risks for CRCI and cognitive aging and whether these endpoints share common pathways.

Biological Measures

Considerable effort has been made to identify biomarkers of the aging process and calculate biological age (41). In the following section, we highlight biological measures discussed at the think tank because of their relevance to several hallmarks of aging (eg, genomic instability, stem cell exhaustion, cellular senescence, inflammation, mitochondrial dysfunction, and epigenetic alterations) and their relationships with cancer treatments and aging-related processes and endpoints.

DNA Damage and Mutation Burden

The frequencies of single nucleotide variants and chromosomal aberrations are modified at varying rates over the life course due to environmental exposures and endogenous processes, including DNA repair capacity (106). In addition to contributing to cancer etiology, these genomic changes also compromise the function of tissues, including those that are largely post-mitotic. For example, the decline in human skeletal muscle function with age might be attributed to amassing somatic mutations in satellite cells (107,108). Higher mutation burden may compromise the ability of these cells to regenerate, remodel, and maintain skeletal muscle mass, resulting in sarcopenia and reduced function. DNA damage has also been associated with exposure to chemotherapy and/or radiation (109,110).

Stem Cell Depletion and Dysfunction

Stem cells play an important role in tissue maintenance and repair in adulthood. Loss of stem cell homeostasis with aging is associated with epigenetic reprogramming, deregulated nutrient sensing, and accumulating DNA damage leading to a loss of self-renewing potential and stem cell exhaustion (111). Stem cell depletion and dysfunction are associated with osteoporosis and sarcopenia due to the loss of mesenchymal and muscle stem cells, respectively (111–113). Reduced diversity of aging hematopoietic stem cells is associated with clonal hematopoiesis and increased risk of a subsequent diagnosis of myeloid or lymphoid neoplasia and increased all-cause mortality (114). Also, stem cell exhaustion has been linked to reduced tolerance of chemotherapy, and specific therapies, such as doxorubicin and daunorubicin, have been shown to induce stem cell exhaustion, DNA damage, telomere attrition, and cellular senescence (115).

P16INK4a

Cellular senescence is a multifaceted cell fate response both to stressful and physiological stimuli. Senescent cells cease proliferation, which is a crucial anticancer mechanism. However, they also develop a robust senescence-associated secretory phenotype that can alter the structure and function of the tissues in which they reside, particularly by increasing inflammation (17). Although there are no senescence-specific biomarkers, there are a dozen or more markers that can identify senescent cells with some confidence. P16INK4a has been associated with a loss of physical function in older adults, affecting mobility, muscle strength, and central obesity (73,116). In mice, the elimination of p16INK4a-positive cells prevents or ameliorates a diverse number of aging-related pathologies, including cancer (117). In prospectively followed breast cancer patients treated with standard adjuvant chemotherapy, p16INK4a expression nearly doubled after they received doxorubicin and cyclophosphamide chemotherapy in an adjuvant setting—equating to more than 14.7 years of chronological aging (8,116). Although measures of cellular senescence are still in their infancy, they demonstrate translational promise to contextualize biological aging in humans.

Inflammatory Markers

Aging is strongly associated with increased inflammation (118–121). Increased systemic levels of proinflammatory cytokines contribute to physiological decline (118–122) and incidence of disease, including cancer and other acute (eg, infection) and chronic conditions. Inflammatory mediators such as interleukin-6, high-sensitivity C-reactive protein, and receptor for advanced glycation end products–related inflammation are biomarkers of susceptibility to frailty, disability, morbidity, and mortality at older ages (123–125). Also, the frequency of senescent cells in tissues increases with age, after genotoxic insults, and after systemic cancer therapy (17). These cells secrete numerous inflammatory cytokines, including interleukin-1β and interleukin-6, as part of the above-described senescence-associated secretory phenotype. Given that increased inflammation and cellular senescence are associated with chemotherapy and radiation (126,127), panels of inflammatory markers could be used to monitor the long-term consequences of cancer treatment.

31Phosphocreatine Recovery Time

Mitochondria are a major source of the chemical energy in cells and are needed both for survival and function. The function of these vital organelles has been shown to decline with age in several tissues, including the brain and skeletal muscle (69), as well as in pancreatic beta cells (70). Diminished mitochondrial function can be measured in numerous ways, including 31Phosphocreatine recovery time, an indicator of mitochondrial capacity in skeletal muscle in humans (71) that has been linked to reduced skeletal muscle strength and decreased walking performance (72).

Epigenetic Age

Changes in the epigenetic state of the genome can affect gene expression, and such epigenomic changes have been identified in aging tissues and cells (78). Epigenetic changes are reversible, and measures of DNA methylation (DNAm) age may help identify or evaluate promising interventions against accelerated or accentuated aging (76). Further, epigenetic age can be measured from blood, a biospecimen that is feasible to collect in large epidemiologic studies. Multitissue DNAm-based measures of biological age, including Horvath's clock (77) and DNAm PhenoAge (78), are promising because they apply to different DNA sources (sorted cells, organs, and tissues) across the life span (76). Hannum's clock, a single-tissue estimator of CpG markers in whole blood, has also been used as a measure of biological age; however, its use may lead to biased estimates in nonblood tissue, and estimates may be subject to confounding from age-related changes in blood composition (74,76,128). DNAm measured in blood has been associated with an increased risk of frailty, physical function, and all-cause mortality (78,128–131). Importantly, accelerated epigenetic aging has also been linked to increased cancer risk and cancer-specific mortality (78,131–135). More research is needed to understand how epigenetic age can be measured longitudinally among cancer survivors and whether it is possible to slow biological aging by targeting age-related DNAm levels.

The Pace of Aging

The Pace of Aging is a composite of repeated measures of 18 biomarkers, including measures of cardiovascular, metabolic, immune, kidney, liver, and lung function, as well as dental health and leukocyte telomere length, which together assesses biological change across organ systems and predicts aging-related processes (136). Among a 1972–1973 birth cohort followed through age 38 years, individuals with a faster Pace of Aging showed evidence of functional deficits and decline (eg, balance, grip strength, motor coordination, physical limitations, cognitive decline, self-reported health, facial aging) (136) and tended to have more psychosocial factors associated with aging-related morbidity (eg, shorter-lived families, low childhood socioeconomic status, and adverse childhood experiences) (137). However, the Pace of Aging has not been tested as a predictor of mortality. Future work is needed to understand the relationship among the Pace of Aging, cancer, cancer treatment, and mortality.

Methodological Considerations

To date, the identification of—and discrimination between—aging trajectories related to cancer and cancer treatment has been hindered by resource capacity limits for sustained accrual, repeated longitudinal assessment, and expanded endpoint surveillance of population-based cohorts of cancer survivors (Box 1). Longitudinal assessments of functional capacity are required to characterize aging trajectories over time. Longitudinal studies that track within-person change can distinguish true

aging (a process of change) from differences between individuals (136,138,139). Moreover, longitudinal studies can account for time-varying exposures, such as weight, diet, exercise, and cigarette smoking, and more precisely observe age, period, and cohort effects.

Tools are needed to identify and predict vulnerable subgroups at risk for developing aging-related consequences of cancer and treatment. Consideration of personal risk and psychosocial factors over the life course is warranted because they affect biological aging and modify aging trajectories (137). Many studies exclude participants with vulnerabilities such as anxiety, depression, lack of social support, and social isolation despite evidence that suggests these vulnerabilities are important for a holistic understanding of functional outcomes at any age (95,97,140). Cancer surveillance systems like the Surveillance, Epidemiology, and End Results Program of the NCI might be leveraged as methodological and infrastructure resources for special studies addressing long-term functional outcomes and adverse treatment effects. Dedicated research infrastructures are needed to harmonize and aggregate data across multiple sources (eg, electronic health records, validated instruments, geospatial and health-care delivery environments).

Opportunities to Expand the Evidence Base for Aging-Related Consequences of Cancer and Cancer Treatment

The objective of the think tank was to discuss empirically justified measures of aging to consider including in studies of aging-related consequences of cancer and cancer treatment. During meeting deliberations, several opportunities to expand the evidence base emerged (Box 2). A better understanding of the mechanisms that contribute to cancer- and treatment-associated aging will advance our efforts to identify aging phenotypes and develop new evidence-based strategies to prevent, mitigate, and slow cancer- and treatment-related effects.

Preclinical Research

Preclinical studies using appropriately aged animals or alternative models of aged human systems (ie, biomimetics) could be used to study cancer and aging processes. Basic science findings from mechanistic studies could lead to novel translational research and new or modified intervention approaches that reduce toxicity and long-term morbidity. As targeted cancer therapies are developed and integrated into clinical care, examining their impacts on aging trajectories of cancer survivors will be paramount.

Clinical Research

Studies of cancer survivors could be designed to provide data on long-term and late-emerging effects of combinations of cancer therapies on aging endpoints. The need to launch adequately powered studies with comprehensive treatment- and aging-related data from cancer survivors with variability by cancer type, treatment, and past exposures was discussed. Think tank participants endorsed a focus on common cancers (eg, breast and prostate) first. Expanding eligibility criteria in clinical trials to include older adults with comorbidities and higher levels of frailty was recommended to assess treatment effects and toxicity (141). Cancer etiology and other epidemiologic cohort studies could be leveraged, but most were not designed to capture detailed cancer treatment, follow-up outcomes (eg, recurrence), or aging endpoints. Incentivizing existing cancer patient or survivor and aging cohort studies to collect aging processes, outcomes, and cancer treatment data, respectively, was discussed as one option to leverage extant research investment infrastructures.

Clinical Practice

Evidence-based clinical assessments of functional capacity collected prior to the initiation of cancer treatments and at regular follow-up intervals thereafter are needed (at minimum) to monitor changes in functional reserve. In addition, an assessment that regularly captures biological, behavioral, and psychosocial factors associated with physical function, such as the GA, is recommended for clinical practice to render a more holistic evaluation of care needs. Clinicians, survivors, and caregivers should be educated on the aging-related consequences of cancer and treatment. A collaborative care model and an infrastructure to support communication between multidisciplinary care teams is needed to monitor changes in health status before the onset of disability and frailty.

Summary of Think Tank Deliberations

Ideal measures would validly and reliably capture underlying processes associated with aging, reflect the degree of functional reserve, and predict aging endpoints (142). At this time, no single existing biomarker or composite measure is sensitive or specific enough to capture biological or functional age accurately, so a multilevel approach is needed to measure aging-related consequences of cancer and its treatments (43). The Fried Frailty Phenotype, deficit accumulation/frailty index, and GA differ in their degree of clinical utility and ability to distinguish levels of frailty among cancer patients; thus, the most appropriate clinical measure to implement depends on specific outcomes of interest, cost, time, and clinical feasibility (Table 1). One important outcome of the meeting was the recommendation that at least one functional measure, such as gait speed or grip strength, should be assessed in clinical studies of cancer survivors. Several promising biological measures are also worthy of future study, including 31Phosphocreatine recovery time (69,70,72), p16INK4a (19,73,116,126), estimators of DNAm age (74–76,79,143,144), and the Pace of Aging (136,137). Other composite measures of biological age have been put forth in recent years (145–151); however, these measures do not distinguish the ongoing process of aging from differences in system integrity present from earlier in life. Additionally, none of the composite measures of biological aging have been studied or validated in cancer survivors.

Some evidence suggests that cancer and its treatments have long-term, unintended aging-related consequences. More research is needed to better assess the rate of aging and to understand the relationships between markers of biological age and functional outcomes in cancer survivors. This report summarized expert-informed deliberations of measures that might be considered for inclusion in research studies of the aging-related consequences of cancer and cancer treatment and highlights gaps in our understanding of the processes that underlie differential responses to cancer treatment. Addressing these research gaps will help inform strategies to enhance healthy aging for all cancer survivors.

Box 2. Preclinical and clinical research opportunities to expand the evidence base for research studies on the aging-related consequences of cancer and cancer treatment

Opportunities for Preclinical Research

- Conduct animal studies using old and young animal models to determine the effects of established and newer cancer therapies on aging endpoints.
- Support mechanistic studies that may lead to novel translational research and new or modified treatments that reduce toxicity and long-term morbidity.
- Support replication studies of animal models to better understand the predictors of functional and cognitive aging processes in the presence of cancer treatments.
- Examine the rate of aging and its impact on tissue microenvironments, including research on the effects of physical activity and dietary restriction on aging outcomes.
- Elucidate the role of cancer treatment in damage to the tissue microenvironment and its relationship to cancer recurrence and drug resistance.
- Develop anticancer agents that attack cancer cells and simultaneously boost the tissue microenvironment to favor the normal cell phenotype.
- Use preclinical models to identify the mechanisms underlying frailty in cancer patients.

Opportunities for Clinical Research

- Include cancer survivors with heterogeneous chronological and functional ages in randomized controlled trials.
- Develop and validate tools for the identification of late-emerging effects and aging phenotypes.
- Test implementation and dissemination of tools to measure aging-related outcomes in clinical practice and their impact on health outcomes.
- Support infrastructure to incorporate clinical assessments at baseline and posttreatment to create personalized risk-stratified care models.
- Design an infrastructure appropriate for a clinical environment that aggregates information derived from a variety of sources (eg, electronic health records, validated instruments, self-report).
- Develop cancer treatment-related, evidence-based practice guidelines for risk prediction, screening, prevention, diagnostics, treatment, and follow-up care.
- Design surveillance systems to monitor cancer patients long-term for adverse events due to cancer medications and therapies.
- Conduct research to understand the relationships between markers of biological age and functional outcomes in cancer survivors.
- Conduct longitudinal epidemiologic studies to better assess the rate of aging, investigate the long-term effects of cancer treatment and combination therapy in cancer survivors, distinguish the major determinants of progressing to an aging phenotype, characterize trajectories of aging, quantify the incidence and severity of aging phenotypes, and identify subgroups of cancer survivors at risk for an "accelerated aging" phenotype.
- Establish standards and evaluation measures using geriatric assessments and biomarkers for surveillance in younger and older cancer survivors.
- Examine whether aging-related processes are involved in the risk of second malignancies after chemotherapy.
- Examine the role of composite measures (eg, the Pace of Aging) as early indicators of aging phenotypes.
- Refine neurocognitive measures to reduce assessment burden and improve feasibility in clinical and research settings, while preserving sensitivity to detect small changes in function. Consider using neuroimaging techniques and blood, plasma, or other fluid biomarkers to elucidate the mechanisms of cancer-related cognitive impairment (CRCI).
- Conduct cross-disciplinary studies both of cancer survivors and noncancer populations with cognitive decline or Alzheimer disease to understand risks for CRCI and cognitive aging.
- Conduct research on resilience as a key predictor, modifier, or outcome of aging processes after cancer treatment.
- Examine the impact of personality types (eg, conscientiousness and optimism) on cancer- and treatment-associated aging.
- Develop evidence from interventions about whether increases in system reserve can mitigate aging processes and improve aging-related functional outcomes.
- Quantify the impact of early intervention (postdiagnosis and treatment) on quality-of-life outcomes in cancer survivors.

Opportunities for Clinical Practice

- Implement evidence-based comprehensive screening and surveillance tools, such as the geriatric assessment, to assess risk for treatment toxicity and establish baseline measures of—and monitor changes in—function and the biological, behavioral, and psychosocial contributors to health outcomes over time.
- Consider incorporating a collaborative care model for the surveillance of aging outcomes.
- Consider including specialists with a clinical background in aging or geriatrics within the multidisciplinary care team.
- Improve education related to the aging consequences of cancer and cancer treatment for clinicians, survivors, and caregivers.

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Notes

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References

1. Parry C, Kent EE, Mariotto AB, Alfano CM, Rowland JH. Cancer survivors: a booming population. *Cancer Epidemiol Biomarkers Prev*. 2011;20(10):1996–2005.
2. DeSantis CE, Lin CC, Mariotto AB, et al. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin*. 2014;64(4):252–271.
3. Henderson TO, Ness KK, Cohen HJ. Accelerated aging among cancer survivors: from pediatrics to geriatrics. *Am Soc Clin Oncol Educ Book*. 2014;e423–e430.
4. Hurria A, Jones L, Muss HB. Cancer treatment as an accelerated aging process: assessment, biomarkers, and interventions. *Am Soc Clin Oncol Educ Book*. 2016;35:e516–e522.
5. Armenian SH, Gibson CJ, Rockne RC, Ness KK. Premature aging in young cancer survivors. *J Natl Cancer Inst*. 2019;111(3):226–232.
6. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100(1):57–70.
7. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194–1217.
8. Sanoff HK, Deal AM, Krishnamurthy J, et al. Effect of cytotoxic chemotherapy on markers of molecular age in patients with breast cancer. *J Natl Cancer Inst*. 2014;106(4):dju057.
9. Gems D, Partridge L. Genetics of longevity in model organisms: debates and paradigm shifts. *Annu Rev Physiol*. 2013;75(1):621–644.
10. Margolick JB, Ferrucci L. Accelerating aging research: how can we measure the rate of biologic aging? *Exp Gerontol*. 2015;64:78–80.
11. Franceschi C, Garagnani P, Morsiani C, et al. The continuum of aging and age-related diseases: common mechanisms but different rates. *Front Med (Lausanne)*. 2018;5:61. doi:10.3389/fmed.2018.00061
12. Ahles TA, Hurria A. New challenges in psycho-oncology research IV: cognition and cancer: conceptual and methodological issues and future directions. *Psychooncology*. 2018;27(1):1–23.
13. Campisi J, d'Adda di Fagagna F. Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol*. 2007;8(9):729–740.
14. Schmitt CA. Cellular senescence and cancer treatment. *Biochim Biophys Acta*. 2007;1775(1):5–20.
15. Kim JH, Jenrow KA, Brown SL. Mechanisms of radiation-induced normal tissue toxicity and implications for future clinical trials. *Radiat Oncol J*. 2014;32(3):103–115.
16. Watt DG, Horgan PG, McMillan DC. Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: a systematic review. *Surgery*. 2015;157(2):362–380.
17. Campisi J. Aging, cellular senescence, and cancer. *Annu Rev Physiol*. 2013;75:685–705.
18. Chang B-D, Swift ME, Shen M, Fang J, Broude EV, Roninson IB. Molecular determinants of terminal growth arrest induced in tumor cells by a chemotherapeutic agent. *Proc Natl Acad Sci USA*. 2002;99(1):389–394.
19. Schmitt CA, Fridman JS, Yang M, et al. A senescence program controlled by p53 and p16INK4a contributes to the outcome of cancer therapy. *Cell*. 2002;109(3):335–346.
20. Coppé J-P, Patil CK, Rodier F, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLoS Biol*. 2008;6(12):2854–2868.
21. Novakova Z, Hubackova S, Kosar M, et al. Cytokine expression and signaling in drug-induced cellular senescence. *Oncogene*. 2010;29(2):273–284.
22. Buttiglieri S, Ruella M, Risso A, et al. The aging effect of chemotherapy on cultured human mesenchymal stem cells. *Exp Hematol*. 2011;39(12):1171–1181.
23. Beeharry N, Broccoli D. Telomere dynamics in response to chemotherapy. *Curr Mol Med*. 2005;5(2):187–196.
24. Diker-Cohen T, Uziel O, Szyper-Kravitz M, Shapira H, Natur A, Lahav M. The effect of chemotherapy on telomere dynamics: clinical results and possible mechanisms. *Leuk Lymphoma*. 2013;54(9):2023–2029.
25. Yoon SY, Sung HJ, Park KH, et al. Telomere length shortening of peripheral blood mononuclear cells in solid-cancer patients undergoing standard-dose chemotherapy might be correlated with good treatment response and neutropenia severity. *Acta Haematol*. 2007;118(1):30–37.
26. Bhakta N, Liu Q, Yeo F, et al. Cumulative burden of cardiovascular morbidity among pediatric, adolescent and young adult Hodgkin lymphoma survivors: an analysis from the St. Jude Lifetime Cohort Study. *Lancet Oncol*. 2016;17(9):1325–1334.
27. Ness KK, Armstrong GT, Kundu M, Wilson CL, Tchkonia T, Kirkland JL. Frailty in childhood cancer survivors. *Cancer*. 2015;121(10):1540–1547.
28. Ness KK, Krull KR, Jones KE, et al. Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. *J Clin Oncol*. 2013;31(36):4496–4503.
29. Krull KR, Hardy KK, Kahalley LS, Schuitema I, Kesler SR. Neurocognitive outcomes and interventions in long-term survivors of childhood cancer. *J Clin Oncol*. 2018;36(21):2181–2189.

30. Ness KK, Bhatia S, Baker KS, et al. Performance limitations and participation restrictions among childhood cancer survivors treated with hematopoietic stem cell transplantation: the Bone Marrow Transplant Survivor Study. *Arch Pediatr Adolesc Med*. 2005;159(8):706–713.
31. Wilson CL, Stratton K, Leisenring WM, et al. Decline in physical activity level in the Childhood Cancer Survivor Study cohort. *Cancer Epidemiol Biomarkers Prev*. 2014;23(8):1619–1627.
32. Howell CR, Wilson CL, Ehrhardt MJ, et al. Clinical impact of sedentary behaviors in adult survivors of acute lymphoblastic leukemia: a report from the St. Jude Lifetime Cohort study. *Cancer*. 2018;124(5):1036–1043.
33. Keating NL, Nørredam M, Landrum MB, Huskamp HA, Meara E. Physical and mental health status of older long-term cancer survivors. *J Am Geriatr Soc*. 2005;53(12):2145–2152.
34. Alfano CM, Peng J, Andridge RR, et al. Inflammatory cytokines and comorbidity development in breast cancer survivors versus noncancer controls: evidence for accelerated aging? *J Clin Oncol*. 2017;35(2):149–156.
35. Hewitt M, Rowland JH, Yancik R. Cancer survivors in the United States: age, health, and disability. *J Gerontol A Biol Sci Med Sci*. 2003;58(1): M82–M91.
36. Gresham G, Dy SM, Zipunnikov V, et al. Fatigability and endurance performance in cancer survivors: analyses from the Baltimore Longitudinal Study of Aging. *Cancer*. 2018;124(6):1279–1287.
37. Wanigatunga A, Gresham G, Martinez-Amezcua P, et al. Contrasting characteristics of daily physical activity in older adults by cancer history. *Cancer*. 2018;124(24):4692–4699.
38. Ahles TA, Root JC. Cognitive effects of cancer and cancer treatments. *Annu Rev Clin Psychol*. 2018;14:425–451.
39. Guralnik JM, Melzer D. Chronological and functional ageing. In: Copeland JRM, Abou-Saleh MT, Blazer DG, eds. *Principles and Practice of Geriatric Psychiatry*. 2nd ed. West Sussex: John Wiley & Sons Ltd; 2002:71–74.
40. Lowsky DJ, Olshansky SJ, Bhattacharya J, Goldman DP. Heterogeneity in healthy aging. *J Gerontol A Biol Sci Med Sci*. 2014;69(6):640–649.
41. Jylhävä J, Pedersen NL, Hägg S. Biological age predictors. *EBioMedicine*. 2017; 21:29–36.
42. Baker GT III, Sprott RL. Biomarkers of aging. *Exp Gerontol*. 1988;23(4–5): 223–239.
43. Soto-Perez-de-Celis E, Li D, Yuan Y, Lau YM, Hurria A. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. *Lancet Oncol*. 2018;19(6):e305–e316.
44. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA*. 2011;305(1):50–58.
45. Studenski S, Perera S, Wallace D, et al. Physical performance measures in the clinical setting. *J Am Geriatr Soc*. 2003;51(3):314–322.
46. Cooper R, Kuh D, Hardy R, Mortality Review Group. Objectively measured physical capability levels and mortality: systematic review and meta-analysis. *BMJ*. 2010;341:c4467.
47. Abellan van Kan G, Rolland Y, Andrieu S, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. *J Nutr Health Aging*. 2009;13(10):881–889.
48. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39(2):142–148.
49. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146–M156.
50. De Vries NM, Staal JB, Van Ravensberg CD, Hobbelen JSM, Rikkert MO, Nijhuis-Van der Sanden M. Outcome instruments to measure frailty: a systematic review. *Ageing Res Rev*. 2011;10(1):104–114.
51. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal*. 2001;1:323–336.
52. Hurria A, Cirrincione CT, Muss HB, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. *J Clin Oncol*. 2011;29(10):1290–1296.
53. Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: a feasibility study. *Cancer*. 2005;104(9):1998–2005.
54. Hurria A, Akiba C, Kim J, et al. Reliability, validity, and feasibility of a computer-based geriatric assessment for older adults with cancer. *J Oncol Pract*. 2016;12(12):e1025–e1034.
55. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the Chemotherapy Risk Assessment Scale for High-age Patients (CRASH) score. *Cancer*. 2012;118(13):3377–3386.
56. Avelino-Silva TJ, Farfel JM, Curiati JA, Amaral JR, Campora F, Jacob-Filho W. Comprehensive geriatric assessment predicts mortality and adverse outcomes in hospitalized older adults. *BMC Geriatr*. 2014;14(1):129. doi: 10.1186/1471-2318-14-129.
57. Jonna S, Chiang L, Liu J, Carroll MB, Flood K, Wildes TM. Geriatric assessment factors are associated with mortality after hospitalization in older adults with cancer. *Support Care Cancer*. 2016;24(11):4807–4813.
58. Sargent-Cox KA, Anstey KJ, Luszcz MA. The relationship between change in self-perceptions of aging and physical functioning in older adults. *Psychol Aging*. 2012;27(3):750–760.
59. Levy BR, Slade MD, Kasl SV. Longitudinal benefit of positive self-perceptions of aging on functional health. *J Gerontol B Psychol Sci Soc Sci*. 2002;57(5): P409–P417.
60. Demakakos P, Biddulph JP, de Oliveira C, Tsakos G, Marmot MG. Subjective social status and mortality: the English Longitudinal Study of Ageing. *Eur J Epidemiol*. 2018;33(8):729–739.
61. Kotter-Grühn D, Kleinspehn-Ammerlahn A, Gerstorf D, Smith J. Self-perceptions of aging predict mortality and change with approaching death: 16-year longitudinal results from the Berlin Aging Study. *Psychol Aging*. 2009; 24(3):654–667.
62. Lai J-S, Wagner LI, Jacobsen PB, Cella D. Self-reported cognitive concerns and abilities: two sides of one coin? *Psychooncology*. 2014;23(10):1133–1141.
63. Wefel JS, Vardy J, Ahles T, Schagen SB. International Cognition and Cancer Task Force recommendations to harmonise studies of cognitive function in patients with cancer. *Lancet Oncol*. 2011;12(7):703–708.
64. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11(3):570–579.
65. Fries JF, Bruce B, Cella D. The promise of PROMIS: using item response theory to improve assessment of patient-reported outcomes. *Clin Exp Rheumatol*. 2005;23(5 suppl 39):S53–S57.
66. Simonsick EM, Schrack JA, Glynn NW, Ferrucci L. Assessing fatigability in mobility-intact older adults. *J Am Geriatr Soc*. 2014;62(2):347–351.
67. Simonsick EM, Glynn NW, Jerome GJ, Shardell M, Schrack JA, Ferrucci L. Fatigued, but not frail: perceived fatigability as a marker of impending decline in mobility-intact older adults. *J Am Geriatr Soc*. 2016;64(6):1287–1292.
68. Deelen J, Beekman M, Uh H-W, et al. Genome-wide association study identifies a single major locus contributing to survival into old age; the APOE locus revisited. *Aging Cell*. 2011;10(4):686–698.
69. Hill S, Van Remmen H. Mitochondrial stress signaling in longevity: a new role for mitochondrial function in aging. *Redox Biol*. 2014;2:936–944.
70. Mulder H, Ling C. Mitochondrial dysfunction in pancreatic beta-cells in Type 2 diabetes. *Mol Cell Endocrinol*. 2009;297(1–2):34–40.
71. Choi S, Reiter DA, Shardell M, et al. 31P magnetic resonance spectroscopy assessment of muscle bioenergetics as a predictor of gait speed in the Baltimore Longitudinal Study of Aging. *J Gerontol A Biol Sci Med Sci*. 2016; 71(12):1638–1645.
72. Zane AC, Reiter DA, Shardell M, et al. Muscle strength mediates the relationship between mitochondrial energetics and walking performance. *Aging Cell*. 2017;16(3):461–468.
73. He S, Sharpless NE. Senescence in health and disease. *Cell*. 2017;169(6): 1000–1011.
74. Hannum G, Guinney J, Zhao L, et al. Genome-wide methylation profiles reveal quantitative views of human aging rates. *Mol Cell*. 2013;49(2):359–367.
75. Booth LN, Brunet A. The aging epigenome. *Mol Cell*. 2016;62(5):728–744.
76. Horvath S, Raj K. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. *Nat Rev Genet*. 2018;19(6):371–384.
77. Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol*. 2013;14(10):R115.
78. Levine ME, Lu AT, Quach A, et al. An epigenetic biomarker of aging for lifespan and healthspan. *Aging*. 2018;10(4):573–591.
79. Liu Z, Kuo P-L, Horvath S, Crimmins E, Ferrucci L, Levine M. A new aging measure captures morbidity and mortality risk across diverse subpopulations from NHANES IV: a cohort study. *PLoS Med*. 2018;15(12):e1002718.
80. Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale. An examination of its reliability and validity in a research setting. *Cancer*. 1984;53(9):2002–2007.
81. Manig L, Käsmann L, Janssen S, Schild SE, Rades D. Simplified comorbidity score and Eastern Cooperative Oncology Group performance score predicts survival in patients receiving organ-preserving treatment for bladder cancer. *Anticancer Res*. 2017;37(5):2693–2696.
82. Rades D, Bolm L, Kaesmann L, Bartscht T. Karnofsky performance score is predictive of survival after palliative irradiation of metastatic bile duct cancer. *Anticancer Res*. 2017;37(2):949–951.
83. Cesari M, Kritchevsky SB, Newman AB, et al. Added value of physical performance measures in predicting adverse health-related events: results from the Health, Aging And Body Composition Study. *J Am Geriatr Soc*. 2009;57(2): 251–259.
84. Fries JF, Lingala B, Siemons L, et al. Extending the floor and the ceiling for assessment of physical function. *Arthritis Rheumatol*. 2014;66(5):1378–1387.
85. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci*. 2007;62(7):722–727.
86. Rockwood K, Mitnitski A. Frailty defined by deficit accumulation and geriatric medicine defined by frailty. *Clin Geriatr Med*. 2011;27(1):17–26.
87. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ*. 2005;173(5):489–495.
88. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381(9868):752–762.
89. Balducci L. Aging, frailty, and chemotherapy. *Cancer Control*. 2007;14(1):7–12.
90. Crow RS, Lohman MC, Titus AJ, et al. Mortality risk along the frailty spectrum: data from the National Health and Nutrition Examination Survey 1999 to 2004. *J Am Geriatr Soc*. 2018;66(3):496–502.
91. Owusu C, Berger NA. Comprehensive geriatric assessment in the older cancer patient: coming of age in clinical cancer care. *Clin Pract (Lond)*. 2014;11(6): 749–762.

92. Soubeyran P, Fonck M, Blanc-Bisson C, et al. Predictors of early death risk in older patients treated with first-line chemotherapy for cancer. *J Clin Oncol*. 2012;30(15):1829–1834.
93. Walter LC, Brand RJ, Counsell SR, et al. Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. *JAMA*. 2001;285(23):2987–2994.
94. Carey EC, Covinsky KE, Lui LY, Eng C, Sands LP, Walter LC. Prediction of mortality in community-living frail elderly people with long-term care needs. *J Am Geriatr Soc*. 2008;56(1):68–75.
95. Mohile SG, Dale W, Somerfield MR, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO guideline for geriatric oncology. *J Clin Oncol*. 2018;36(22):2326–2347.
96. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol*. 2014;32(24):2595–2603.
97. Mohile SG, Velarde C, Hurria A, et al. Geriatric assessment-guided care processes for older adults: a Delphi consensus of geriatric oncology experts. *J Natl Compr Canc Netw*. 2015;13(9):1120–1130.
98. Hurria A, Mohile S, Gajra A, et al. Validation of a prediction tool for chemotherapy toxicity in older adults with cancer. *J Clin Oncol*. 2016;34(20):2366–2371.
99. Rockwood K, Howlett SE, MacKnight C, et al. Prevalence, attributes, and outcomes of fitness and frailty in community-dwelling older adults: report from the Canadian Study of Health and Aging. *J Gerontol A Biol Sci Med Sci*. 2004;59(12):1310–1317.
100. Ahles TA, Saykin AJ, McDonald BC, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. *J Clin Oncol*. 2010;28(29):4434–4440.
101. Ahles TA, Root JC, Ryan EL. Cancer-and cancer treatment–associated cognitive change: an update on the state of the science. *J Clin Oncol*. 2012;30(30):3675–3686.
102. Mandelblatt JS, Small BJ, Luta G, et al. Cancer-related cognitive outcomes among older breast cancer survivors in the Thinking and Living With Cancer Study. *J Clin Oncol*. 2018;36(32):3211–3222.
103. Horowitz TS, Suls J, Treviño M. A call for a neuroscience approach to cancer-related cognitive impairment. *Trends Neurosci*. 2018;41(8):493–496.
104. van Westrhenen A, Smidt LCA, Seute T, et al. Diagnostic markers for CNS lymphoma in blood and cerebrospinal fluid: a systematic review. *Br J Haematol*. 2018;182(3):384–403.
105. Ahles TA, Li Y, McDonald BC, et al. Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: the impact of APOE and smoking. *Psychooncology*. 2014;23(12):1382–1390.
106. Langie SA, Koppen G, Desaulniers D, et al. Causes of genome instability: the effect of low dose chemical exposures in modern society. *Carcinogenesis*. 2015;36(suppl 1):S61–S88.
107. Almada AE, Wagers AJ. Molecular circuitry of stem cell fate in skeletal muscle regeneration, ageing and disease. *Nat Rev Mol Cell Biol*. 2016;17(5):267–279.
108. Franco I, Johansson A, Olsson K, et al. Somatic mutagenesis in satellite cells associates with human skeletal muscle aging. *Nat Commun*. 2018;9(1):800–811.
109. Scuric Z, Carroll JE, Bower JE, et al. Biomarkers of aging associated with past treatments in breast cancer survivors. *NPJ Breast Cancer*. 2017;3(1):50.
110. Carroll JE, Van Dyk K, Bower JE, et al. Cognitive performance in survivors of breast cancer and markers of biological aging. *Cancer*. 2019;125(2):298–306.
111. Aunon JR, Cho WC, Soreide K. The biology of aging and cancer: a brief overview of shared and divergent molecular hallmarks. *Aging Dis*. 2017;8(5):628–642.
112. Sousa-Victor P, Muñoz-Cánoves P. Regenerative decline of stem cells in sarcopenia. *Mol Aspects Med*. 2016;50:109–117.
113. Noronha-Matos JB, Coerreia-de-Sa P. Mesenchymal stem cells ageing: targeting the "purinome" to promote osteogenic differentiation and bone repair. *J Cell Physiol*. 2016;231(9):1852–1861.
114. Bowman RL, Busque L, Levine RL. Clonal hematopoiesis and evolution to hematopoietic malignancies. *Cell Stem Cell*. 2018;22(2):157–170.
115. Cupit-Link MC, Kirkland JL, Ness KK, et al. Biology of premature ageing in survivors of cancer. *ESMO Open*. 2017;2(5):e000250.
116. Liu Y, Sanoff HK, Cho H, et al. Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. *Aging Cell*. 2009;8(4):439–448.
117. Baker DJ, Childs BG, Durik M, et al. Naturally occurring p16(Ink4a)-positive cells shorten healthy lifespan. *Nature*. 2016;530(7589):184–189.
118. Shaw AC, Joshi S, Greenwood H, Panda A, Lord JM. Aging of the innate immune system. *Curr Opin Immunol*. 2010;22(4):507–513.
119. Caruso C, Lio D, Cavallone L, Franceschi C. Aging, longevity, inflammation, and cancer. *Ann N Y Acad Sci*. 2004;1028(1):1–13.
120. Green DR, Galluzzi L, Kroemer G. Mitochondria and the autophagy–inflammation–cell death axis in organismal aging. *Science*. 2011;333(6046):1109–1112.
121. Krabbe KS, Pedersen M, Bruunsgaard H. Inflammatory mediators in the elderly. *Exp Gerontol*. 2004;39(5):687–699.
122. Goto M. Inflammaging (inflammation+ aging): a driving force for human aging based on an evolutionarily antagonistic pleiotropy theory? *Bioscience Trends*. 2008;2(6):218–230.
123. Sebastiani P, Thyagarajan B, Sun F, et al. Biomarker signatures of aging. *Aging Cell*. 2017;16(2):329–338.
124. Puzianowska-Kuźnicka M, Owczarz M, Wieczorowska-Tobis K, et al. Interleukin-6 and C-reactive protein, successful aging, and mortality: the PolSenior study. *Immun Ageing*. 2016;13(1):21.
125. Lin L, Park S, Lakatta EG. RAGE signaling in inflammation and arterial aging. *Front Biosci (Landmark Ed)*. 2009;14:1403–1413.
126. Demaria M, O'Leary MN, Chang J, et al. Cellular senescence promotes adverse effects of chemotherapy and cancer relapse. *Cancer Discov*. 2017;7(2):165–176.
127. Hämäläinen S, Kuittinen T, Matinlauri I, Nousiainen T, Koivula I, Jantunen E. Neutropenic fever and severe sepsis in adult acute myeloid leukemia (AML) patients receiving intensive chemotherapy: causes and consequences. *Leuk Lymphoma*. 2008;49(3):495–501.
128. Marioni RE, Shah S, McRae AF, et al. DNA methylation age of blood predicts all-cause mortality in later life. *Genome Biol*. 2015;16(1):25.
129. Marioni RE, Shah S, McRae AF, et al. The epigenetic clock is correlated with physical and cognitive fitness in the Lothian Birth Cohort 1936. *Int J Epidemiol*. 2015;44(4):1388–1396.
130. Breitling LP, Saum K-U, Perna L, Schöttker B, Holleczek B, Brenner H. Frailty is associated with the epigenetic clock but not with telomere length in a German cohort. *Clin Epigenet*. 2016;8(1):21.
131. Kresovich JK, Xu Z, O'Brien KM, Weinberg CR, Sandler DP, Taylor JA. Methylation-based biological age and breast cancer risk. *J Natl Cancer Inst*. 2019;111(10):djz020.
132. Zheng Y, Joyce BT, Colicino E, et al. Blood epigenetic age may predict cancer incidence and mortality. *EBioMedicine*. 2016;5:68–73.
133. Durso DF, Bacalini MG, Sala C, et al. Acceleration of leukocytes' epigenetic age as an early tumor and sex-specific marker of breast and colorectal cancer. *Oncotarget*. 2017;8(14):23237–23245.
134. Levine ME, Hosgood HD, Chen B, Absher D, Assimes T, Horvath S. DNA methylation age of blood predicts future onset of lung cancer in the Women's Health Initiative. *Aging* (Albany NY). 2015;7(9):690–700.
135. Ambatipudi S, Horvath S, Perrier F, et al. DNA methylome analysis identifies accelerated epigenetic ageing associated with postmenopausal breast cancer susceptibility. *Eur J Cancer*. 2017;75:299–307.
136. Belsky DW, Caspi A, Houts R, et al. Quantification of biological aging in young adults. *Proc Natl Acad Sci USA*. 2015;112(30):E4104–E4110.
137. Belsky DW, Caspi A, Cohen HJ, et al. Impact of early personal-history characteristics on the Pace of Aging: implications for clinical trials of therapies to slow aging and extend healthspan. *Aging Cell*. 2017;16(4):644–651.
138. Belsky DW, Moffitt TE, Cohen AA, et al. Eleven telomere, epigenetic clock, and biomarker-composite quantifications of biological aging: do they measure the same thing? *Am J Epidemiol*. 2018;187(6):1220–1230.
139. Moffitt TE, Belsky DW, Danese A, Poulton R, Caspi A. The Longitudinal Study of Aging in Human Young Adults: knowledge gaps and research agenda. *J Gerontol A Biomed Sci Med Sci*. 2017;72(2):210–215.
140. Rapaport MH, Maddux RE. Challenges in the development of clinical trials for major depressive disorder: lessons learned from trials in minor depression. *Dialogues Clin Neurosci*. 2002;4(4):402–407.
141. Levit LA, Singh H, Klepin HD, Hurria A. Expanding the evidence base in geriatric oncology: action items from an FDA-ASCO workshop. *J Natl Cancer Inst*. 2018;110(11):1163–1170.
142. Hubbard JM, Jatoi A. Incorporating biomarkers of frailty and senescence in cancer therapeutic trials. *J Gerontol A Biomed Sci Med Sci*. 2015;70(6):722–728.
143. Liao P, Ostrom QT, Stetson L, Barnholtz-Sloan JS. Models of epigenetic age capture patterns of DNA methylation in glioma associated with molecular subtype, survival, and recurrence. *Neuro-Oncology*. 2018;20(7):942–953.
144. Marwitz S, Heinbockel L, Scheufele S, et al. Fountain of youth for squamous cell carcinomas? On the epigenetic age of non-small cell lung cancer and corresponding tumor-free lung tissues. *Int J Cancer*. 2018;143(12):3061–3070.
145. Klemera P, Doubal S. A new approach to the concept and computation of biological age. *Mech Ageing Dev*. 2006;127(3):240–248.
146. Gruenewald TL, Seeman TE, Ryff CD, Karlamangla AS, Singer BH. Combinations of biomarkers predictive of later life mortality. *Proc Natl Acad Sci USA*. 2006;103(38):14158–14163.
147. Cohen AA, Milot E, Li Q, et al. Detection of a novel, integrative aging process suggests complex physiological integration. *PLoS One*. 2015;10(3):e0116489.
148. Levine ME. Modeling the rate of senescence: can estimated biological age predict mortality more accurately than chronological age? *J Gerontol A Biomed Sci Med Sci*. 2013;68(6):667–674.
149. Wiley JF, Bei B, Bower JE, Stanton AL. Relationship of psychosocial resources with allostatic load: a systematic review. *Psychosom Med*. 2017;79(3):283–292.
150. Seeman TE, McEwen BS, Rowe JW, Singer BH. Allostatic load as a marker of cumulative biological risk: MacArthur Studies of Successful Aging. *Proc Natl Acad Sci USA*. 2001;98(8):4770–4775.
151. Szanton SL, Allen JK, Seplaki CL, Bandeen-Roche K, Fried LP. Allostatic load and frailty in the Women's Health and Aging studies. *Biol Res Nurs*. 2008;10(3):248–256.