

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 phase-shift 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, bi-directional 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 lifespan 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 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 to 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) both manifestations and mechanisms should be detected at a younger age than usual.”¹⁰ Evidence from preclinical models shows that radiation^{13,14} 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.^{3,5,26–29} Furthermore, observational studies have shown that survivors of adult-onset cancers have a higher burden of mobility limitations,^{30,31} comorbid conditions,^{32–34} and pain,³⁴ and a greater risk of functional and cognitive impairments compared to 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 (i.e., NCI and National Institute on Aging) and academic representatives. Arti Hurria, M.D., of the City of Hope, and Jennifer Schrack, Ph.D., 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, while 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-upon 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 aging-related endpoints. **Table 1** presents measures of aging to consider

in studies of aging-related consequences of 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

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 (ADL) and Instrumental Activities of Daily Living (IADL). In oncology settings, the Eastern Cooperative Oncology Group (ECOG) and Karnofsky performance status scales are frequently used and are predictive of cancer survival.^{44–46} 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.^{47–49}

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 statuses.⁵⁰ Ceiling effects often occur in younger, healthier cancer survivors, while floor effects typically are observed in the oldest, non-ambulatory patients. This challenge could be addressed with sequential testing, in which all participants are first tested using a validated, basic measure of function (e.g., 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 (e.g., 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,^{51–56} including the use of clinical judgment,⁵⁵ rule-based approaches defined by the presence of symptoms (e.g., Fried Frailty Phenotype),⁵⁴ and calculating the number of deficits (e.g. the deficit accumulation/frailty index or GA).⁵³ The Fried Frailty Phenotype, deficit accumulation/frailty index, and GA predict functional decline, hospitalization rates, and mortality^{27,52,54,56–59} (although the GA-mortality association in cancer survivors is less studied).^{60–63} The GA assesses multiple domains of illness and health, including functional status, comorbidity, nutritional status, cognition, social support, polypharmacy, and psychological state (e.g., depression, anxiety, and distress),^{64–66} and is predictive of chemotherapy toxicity and survival in geriatric oncology samples.^{43,66,67} Recently, the American Society of Clinical Oncology recommended GA for cancer patients ≥ 65 years receiving chemotherapy.⁶⁴

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 mid-life 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.⁶⁸

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, while 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.^{38,69–71} 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 (e.g., colon, prostate, lymphoma, and testicular) and treatment modalities (cranial and non-CNS radiation, endocrine, and hormone ablation therapies).⁷⁰ Cognitive domains affected by a variety of cancer treatment modalities include memory (i.e., working and recognition), processing speed, attention, and executive function.⁷⁰ To facilitate comparison across studies, the International Cognition and Cancer Task Force recommends use of the Hopkins Verbal Learning Test-Revised (learning and memory), Controlled Oral Word Association Test (verbal fluency and executive function), and the Trail Making Test (executive function) to assess cancer-related cognitive impairment (CRCI).⁷² Think tank participants reflected on using self-reported measures (e.g., Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) and the Patient-Reported Outcomes Measurement Information System (PROMIS)[®] Cognitive Function and Cognitive Function-Abilities),^{73,74} 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 impacted by cancer and cancer treatment exposures.⁷⁵

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.⁷⁶

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 APOE4 gene polymorphism, the strongest genetic risk factor for Alzheimer's disease (AD), are more susceptible to cancer-related cognitive decline than those with other APOE genotypes.^{69,71,77} These observations suggest that gene-treatment interactions may accelerate brain aging or impact intermediate aging processes that in turn influence cognition. Cross-disciplinary studies of both cancer survivors and non-cancer populations with cognitive decline or AD could be leveraged to understand risks for CRCI, 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 due to their relevance to several hallmarks of aging (e.g., 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.⁷⁸ 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.^{79,80} 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.^{81,82}

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.⁸³ Stem cell depletion and dysfunction are associated with osteoporosis and sarcopenia, due to the loss of mesenchymal and muscle stem cells, respectively.^{83–85} 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.⁸⁶ 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.⁸⁷

P16INK4a. Cellular senescence is a multifaceted cell fate response to both stressful and physiological stimuli. Senescent cells cease proliferation, which is a crucial anti-cancer mechanism. However, they also develop a robust senescence-associated secretory phenotype (SASP) 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, impacting mobility, muscle strength, and central obesity.^{88,89} In mice, the elimination of p16INK4a-positive cells prevents or ameliorates a diverse number of aging-related pathologies, including cancer.⁹⁰ 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 over 14.7 years of chronological aging.^{8,89} 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.^{91–94} Increased systemic levels of pro-inflammatory cytokines contribute to physiological decline^{91–95} and incidence of disease, including cancer and other acute (e.g., infection) and chronic conditions. Inflammatory mediators such as interleukin-6 (IL-6), high-sensitivity C-reactive protein (hs-CRP), and receptor for advanced glycation end products (RAGE)-related

inflammation are biomarkers of susceptibility to frailty, disability, morbidity, and mortality at older ages.^{96–98} 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 IL-1 β and IL-6, as part of the above-described SASP. Given that increased inflammation and cellular senescence are associated with chemotherapy and radiation,^{99,100} panels of inflammatory markers could be used to monitor the long-term consequences of cancer treatment.

31Phosphocreatine (31p) Recovery Time. Mitochondria are a major source of the chemical energy in cells and are needed for both 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,¹⁰¹ as well as in pancreatic beta cells.¹⁰² Diminished mitochondrial function can be measured in numerous ways, including 31p recovery time, an indicator of mitochondrial capacity in skeletal muscle in humans¹⁰³ that has been linked to reduced skeletal muscle strength and decreased walking performance.¹⁰⁴

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.^{108,108} Epigenetic changes are reversible, and measures of DNA methylation (DNAm) age may help identify or evaluate promising anti-accelerated/acceluated aging interventions.¹⁰⁶ Further, epigenetic age can be measured from blood, a biospecimen that is feasible to collect in large epidemiologic studies. Multi-tissue DNAm-based measures of biological age, including Horvath's clock¹⁰⁷ and DNAm PhenoAge,¹⁰⁸ are promising as they apply to different DNA sources (sorted cells, organs,

and tissues) across the lifespan.¹⁰⁶ 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 non-blood tissue, and estimates may be subject to confounding from age-related changes in blood composition.^{106,109,110} DNAm measured in blood has been associated with an increased risk of frailty, physical function, and all-cause mortality.^{108,110–113} Importantly, accelerated epigenetic aging has also been linked to increased cancer risk and cancer-specific mortality.^{108,113–117} 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.¹¹⁸ Among a 1972-1973 birth cohort followed through 38 years of age, individuals with a faster Pace of Aging showed evidence of functional deficits and decline (e.g., balance, grip strength, motor coordination, physical limitations, cognitive decline, self-reported health, facial aging),¹¹⁸ and tended to have more psychosocial factors associated with aging-related morbidity (e.g., shorter-lived families, low childhood SES, and adverse childhood experiences).¹¹⁹ However, the Pace of Aging has not been tested as a predictor of mortality. Future work is needed to understand the relationship between 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.^{118,120,121} 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, as they impact biological aging and modify aging trajectories.¹¹⁹ 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.^{64,66,122} Cancer surveillance systems like the Surveillance, Epidemiology, and End Results (SEER) 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 (e.g., 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 (i.e., 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 (e.g., 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.¹²³ Cancer etiology and other epidemiologic cohort studies could be leveraged, but most were not designed to capture detailed cancer treatment, follow-up outcomes (e.g., recurrence), or aging endpoints. Incentivizing existing cancer patient/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 prior to 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.¹²⁴ 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 31p recovery time,^{101,102,104} p16INK4a,^{19,88,89,99} estimators of DNA methylation age,^{105–107,109,125,126} and the Pace of Aging.^{118,119} Other composite measures of biological age have been put forth in recent years;^{127–133} 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 related to 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.

Funding

This work was supported by the National Institutes of Health (R01CA172119, R01CA129769, U54CA137788, and P30CA008748 to T.A.A., R01CA180175 to J.D., R21AG054849 to N.G., R01CA174794 and R01CA215405 to K.K., R35CA197289 to J.M., R01CA200859 to N.P., P30AG021334, R21AG053198, and U01AG057545 to J.S., R01AG052964 to R.T.); the Jacobs Foundation (D.W.B.); and the American Association for Cancer Research (J.D.).

Notes

Funds from the National Cancer Institute (NCI) were used to convene experts for the think tank that partially informed the manuscript's scientific scope. NCI and National Institute on Aging staff had roles in the design of the think tank; contributed to the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication. Moreover, the manuscript was reviewed and approved for submission through the NCI Division of Cancer Control and Population Sciences manuscript clearance process.

There are no conflicts of interest to disclose.

The Cancer and Accelerated Aging Scientific Steering Committee dedicates this paper to the memory of Dr. Arti Hurria (1970-2018). Dr. Hurria was an internationally recognized leader who devoted her career to improving the lives of her patients. She was a cherished and highly respected member of our community who shaped the field of geriatric oncology and the work that went into this publication. We mourn her loss and strive to honor her legacy.

We thank Andy Burnett, Kevin Howcroft, and Felipe Sierra for their valuable leadership and scientific contributions to the think tank. We thank Erwin Tan for his presentation on self-perceptions of aging and health. We acknowledge Margaux Henquinet for her meticulous and constructive copyediting contributions to the manuscript.

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Tables

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 (48). Studenski, et al., 2003 (49). Cooper, et al., 2010 (134). Van Kan, et al., 2009 (135). Podsiadlo, et al., 1991 (136).
Timed Up and Go	Podsiadlo, et al., 1991 (136).
Grip Strength	Cooper, et al., 2010 (134).
Fried (CHS) Frailty Phenotype	Fried, et al., 2001 (54). De Vries, et al., 2011 (56).
Deficit Accumulation Index/ Frailty Index	Mitnitski, et al., 2001 (53). De Vries, et al., 2011 (56).
Clinical Geriatric Assessment	Hurria, et al., 2011 (137). Hurria, et al., 2005 (138). Hurria, et al., 2016 (139). Extermann, et al., 2012 (140). Avelino-Silva, et al., 2014 (141). Jonna, et al., 2016 (142).
Self-Rated Health	Sargent-Cox, et al., 2012 (143). Levy, et al., 2002 (144). Demakakos, et al., 2018 (145). Kotter- Grünh, et al., 2009 (146). Lai, et al., 2014 (147).
Cognitive Assessments	
Hopkins Verbal Learning Test-Revised	Wefel, et al., 2011 (72).
Controlled Oral Word Association Test	
The Trail Making Test	
Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog)	Fries, et al., 2005 (73).
PROMIS Cognitive Function and Cognitive Function – Abilities	Cella, et al., 1993 (74).
Fatigability	Simonsick, et al., 2014 (148). Simonsick, et al., 2016 (149). Gresham, et al., 2018 (150). Deelan, et al., 2011 (151).
Apolipoprotein E4 (APOE4)	
31p Recovery Time	Hill, et al., 2014 (101). Mulder, et al., 2009 (102). Choi, et al., 2016 (103). Zane, et al., 2017 (104).
P16INK4a	He, et al., 2017 (88).

Hannum's Clock (DNA Methylation)

Hannum, et al., 2013 (109).

Horvath's Clock (DNA Methylation)

Booth, et al., 2016 (105).

Horvath, et al., 2018 (106).

Horvath, 2013 (107).

PhenoAge (DNA Methylation)

Levine, et al., 2018 (108).

Liu, et al., 2018 (152).

*This table provides a list of measures to capture heterogeneity in aging processes and aging-related functional outcomes. While some measures can be used independently, others, such as the geriatric assessment, require compilation into a composite variable.

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, pooled datasets or consortia, and conduct initial study of common cancers (e.g., breast and prostate) in order 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).

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 anti-cancer 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 post-treatment to create personalized risk-stratified care models.
- Design an infrastructure appropriate for a clinical environment that aggregates information derived from a variety of sources (e.g., 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 (e.g. 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-relevant cognitive impairment (CRCI).
- Conduct cross-disciplinary studies of both cancer survivors and non-cancer populations with cognitive decline or Alzheimer's 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 (e.g., 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 (post-diagnosis 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.

Figure title and legend

Figure 1. Hypothesized Trajectories of Aging-Related Consequences of Cancer and Cancer Treatment.

