# Measuring Aging and Identifying Aging Phenotypes in Cancer Survivors

MEETING SUMMARY FROM NCI THINK TANK #1

JULY 25–26, 2018

Contents

## Executive Summary

**Introduction**

The population of older cancer patients and survivors has increased in recent decades. Much of this growth may be attributed to successes in cancer detection, diagnosis, and therapy, as well as a demographic shift toward an older population. As cancer therapies advance and more cancer survivors are living longer, the focus of the research community is expanding to include not only survival but also disability risk, quality of life, functional ability, and other more nuanced outcomes. However, the issues and health outcomes unique to this population remain underrepresented in research.

Oncologists have witnessed the impact of cancer and cancer treatment on the aging trajectory of cancer survivors, primarily from anecdotal evidence and interactions with patients and their families. While some patients may return to a healthy state after a cancer diagnosis and treatment, some never fully recover and appear to be placed on an altered aging trajectory. It is crucial to discern whether these cancer survivors experience a poorer trajectory of aging (relative to their pre-cancer state) or if they are entering a state of accelerated aging. And, if their aging trajectory has been modified, are there preventive measures or interventions that can allow these survivors to live longer, higher-quality, disability-free lives?

> **BOX 1: OVERARCHING MEETING OBJECTIVES**
>
> 1. How do we define aging trajectories in a cancer survivorship context?
>
> 2. What is known regarding the measurement and identification of aging phenotypes in cancer survivors?
>
> 3. Are there any gaps in knowledge that limit research and the clinical community from measuring and identifying these phenotypes?

This meeting was the first in a series of think tank meetings supported by the National Cancer Institute's Division of Cancer Control and Population Sciences. It was convened to discuss measurement and identification of aging phenotypes in cancer survivors. Specifically, the objectives of the meeting were to answer the questions outlined in **Box 1**.

**Key Findings**

Several concepts emerged through group deliberation, and key findings and research gaps are summarized by topic area as follows.

1. **Aging Trajectories.** It is important to fully understand the trajectories of aging after cancer diagnosis and treatment. Particularly, after the initial "hit" of cancer and associated treatment, do individuals experience a paralleled "normal" aging trajectory with weakened reserve (Phase Shift/Accentuated Aging Hypothesis), or an altered aging trajectory with quicker progression to aging phenotypes (Accelerated Aging Hypothesis)?

2. **Validated instruments.** Although many measures are available to quantify aging, certain validated measures, indices, and batteries were highlighted during the meeting as important tools for systematic collection of aging markers. These instruments include the Comprehensive Geriatric Assessment, the Frailty Index, the "Pace of Aging," functional performance batteries, and neurocognitive batteries.

3. **An emphasis on longitudinal studies.** Many presenters and discussants noted the importance of employing longitudinal studies in aging research. These types of studies address temporal challenges associated with differential environmental exposures over time that may not be controlled for in cross-sectional studies. To address possible issues with study length, intermediate endpoints, such as biomarkers of biological aging, may be used instead of mortality, although future study in a cancer context is warranted.

4. **Depth and breadth of data.** When faced with finite funding, researchers often face a choice: 1) to enroll a large sample to ensure sufficient study power but reduce the number of measures or study length; or 2) to enroll a smaller sample size but collect a wide range of multimodal measures. This

tradeoff (i.e., power vs. depth) was discussed in the context of aging research in cancer survivors, particularly when detecting early-life signals of accelerated aging.

5. **Applicability of measures to younger and older cancer survivors.** Some measures, such as the Comprehensive Geriatric Assessment and the Frailty Index, are associated with the evaluation and treatment of older adults. However, younger cancer survivors experience frailty at high rates. Expanding the application of these assessments to all cancer survivors presents a new set of challenges, including reaching the ceiling or floor of detection, where healthy or highly disabled participants may not be adequately measured, hindering the ability to detect subtle signals of aging. Modification of these measures to include younger populations increases their applicability in both research and clinical settings.

6. **Sequential measures.** There are several concerns associated with using many indices or batteries of aging, including ceiling and floor effects and participant (or patient) burden, as some measures require multi-part tests or surveys. These challenges may be addressed with sequential testing, in which all participants are tested using a basic measure. If patients perform at or over the ceiling or floor of detection, then they are given a subsequent test to further discriminate ability.

7. **Clinical relevance and feasibility.** The interplay between research and clinical care is a key component of aging research. Measures or markers of aging that are valuable in a research setting may not be feasible to implement or interpret in a clinical context. These research-specific measures can be used as tools to validate clinical measures, so that evidence-based recommendations can be made to cancer survivors receiving care.

## Systems Science

### *The Power of Data*

Multifactor, large datasets can provide unique insights into individual patterns of aging in cancer survivors. This type of data can be used to examine predictors of advanced biological age, such as the presence of chronic disease (e.g., cancer), clinical biomarkers, or metabolic pathways. Deviations in these types of measures can be compared to a larger, "healthy" population prior to a disease event to gain insight into the rate of aging and its early stage predictors.

| BOX 2: SYSTEMS SCIENCE RESEARCH GAPS |
| --- |
| 1. *Practical and Applied Considerations:* <br> a. How do we practically implement a systems science approach in cancer research? <br><br> b. Can we use a systems science approach with extant data resources (e.g., cancer cohorts)? <br><br> c. How do we ensure that the oldest and sickest are included in our studies that use the systems science approach? <br><br> 2. *Measurement and Design Considerations:* <br> a. How do we conceptualize/measure/distinguish between population trends/rates of aging versus individual (biological) systems of aging? Does this employ a longitudinal within person design? <br><br> b. How do we measure accumulation/loss of redundancy? <br><br> c. How do we measure the rate of aging? Are individual biomarkers enough, or do we need a systems science approach? <br><br> d. Is aging linear or non-linear? Is it person-dependent? Is it driven by survival bias? <br><br> 3. *Definitions:* <br> a. How do we define tipping points? <br><br> b. How do we define the transition from normal aging to accelerated aging within cancer survivorship? <br><br> 4. *Redundancy and Resiliency:* <br> a. How do we capture small changes and the ability to return to normal quickly when studying the aging of systems? <br><br> b. How does the redundancy model of aging account for intra-system dependency? <br><br> c. There are issues related to competing risks of degradation failures due to treatment exposures. How do we minimize the degradation failures of other systems? |

### Reliability Theory

Biological systems are considered a series-parallel system with distributed redundancy, in which vital organs are connected in series, but cells within vital organs are connected in parallel. Aging-related changes may be attributed to accumulated cell loss (i.e., cumulative damage) in this highly redundant system over time. The High Initial Damage Load (HIDL) hypothesis suggests that people who develop cancer may be initially vulnerable or have higher rates of accrued damage from birth. Highly sensitive measures should be developed to detect this early-life damage and disentangle initial vulnerability from the effects of cancer and treatment.

**Box 2** outlines research gaps in systems science and accelerated aging in cancer survivors.

## Clinical Markers of Aging

### Staging the Aging

The Comprehensive Geriatric Assessment combines validated instruments with clinical evaluation to assess a patient's functional status, comorbidities, cognition, nutritional status, psychosocial status, and medication status. These measures can be used to calculate the Deficit Accumulation Index, which has been found to be predictive of outcomes such as frailty, toxicity, and re-hospitalization. Presenters defined resilience as "the ability of an organism to appropriately respond to a stress and return to basal physiology," although multiple variations of this definition are in use. The assessment of resilience is critical to the full understanding of geriatric patients; however, measures of resilience need to be developed and refined so they may be clinically relevant.

### Functional Performance Measures

Functional performance measures provide a valuable way to characterize the functional effects of aging and may represent natural constellations or batteries of individual aging markers. In particular, gait speed has been found to be predictive of many health outcomes and is feasible to assess in both research and clinical settings. More difficult tests can be used to assess an individual's physiologic reserve, or to test younger, healthier individuals who may be at or near the ceiling of detection for standard functional tests.

**Box 3** outlines research gaps in clinical markers of aging in cancer survivors.

> **BOX 3: CLINICAL MARKERS OF AGING RESEARCH GAPS**
>
> 1. *Practical and Applied Considerations:*
>    a. How do we establish population-based samples of cancer survivors to define cancer-specific aging phenotypes?
>    b. How do we initiate/follow cohorts that are large enough to parse out effects of specific cancers and treatments?
>    c. How do we create models to account for stressors-upon-stressors (e.g., comorbidities, cancer, functional disabilities)?
>    d. Can we use adaptive designs to facilitate conducting longitudinal cohorts?
>
> 2. *Reserve and Resiliency:*
>    a. How do we best measure physical and cognitive reserve in research and clinical settings?
>    b. Instead of accelerated aging, should we study physical resilience?
>    c. Is the absence of deficits equivalent to resilience?
>    d. Should deficits be divided into two categories: functional and multi-morbid?
>
> 3. *Physical Function:*
>    a. Can we test whether treatments affect function differently by comparing the slopes/rates of change/decline?
>    b. Are there specific cognitive domains that are associated with slow functional performance (walking speed)?
>    c. What basic measures of aging should be included in any study of accelerated aging and cancer?

## Biological Aging Markers and Phenotypes

### *Understanding Aging and Cancer*

Aging, often defined as a biological system's accumulation of deficits, begins early in life. Early-life deficit accumulation can have lifelong impacts, which may influence the rate of aging over time. Therefore, intervention efforts during this period may yield lifelong benefits.

Use of molecular markers of aging is key to understanding aging across the life course. However, early signals of aging are often difficult to detect, because early changes in molecular endpoints are weakly related to clinical outcomes. As the individual ages, phenotypic endpoints, such as muscle strength and walking speed, become increasingly related to clinical outcomes. Finally, late changes in functional endpoints (often the "last to go") are strongly related to clinical outcomes.

Cancer may be described using a similar paradigm to the process of aging. There is high variability in the number and type of mutations that are needed for cancer initiation, yet all cancers show very similar age dependency, apparently due to selection by the tissue microenvironment. In early life and reproductive years, humans have many protective pathways to ensure that pre-cancerous cells do not proliferate in tissue, despite the accumulation of mutations. These protective pathways are at least partly driven by stem cell activity, the quality of which is driven in part by the stem cell niche. However, the tissue microenvironment is impacted by exposures, including lifestyle (e.g., smoking, physical activity) and cancer treatment, as well as by aging itself. Thus, later in life, stem cells may have lower fitness in the degraded tissue environment, leading to expansion of pre-cancerous cells adaptive to this altered environment. The risk of cancer might be better viewed as the rate of loss of these maintenance programs, coupled with the rate of changes in the tissue microenvironment.

### *Approach to Research*

Longitudinal studies permit assessment of aging trajectories of functional capacity over time, deepening our understanding of the pathways involved in aging. Meeting participants discussed the utility of an index to measure accelerated aging, similar to other indices (e.g., the Frailty Index or the Veterans Aging Cohort Study (VACS) Index). The "Pace of Aging" is a composite measure of 18 biomarkers that have been shown to be associated with functional measures in the general population. Further research is needed to determine if such a measure could be adapted to cancer survivors, as it may be difficult to disentangle the effects of aging from cancer and its treatment. The "Hallmarks of Aging" paper provides a useful framework to assess progression to aging phenotypes. While research is ongoing, the 31phosphocreatine (31p) recovery time (PCr), as a measure of mitochondrial function, is the closest to being validated for research and clinical use.

**BOX 4: BIOLOGICAL AGING MARKERS AND PHENOTYPES RESEARCH GAPS**

1. Early changes in biological endpoints weakly relate to clinical outcomes, mid-level changes in phenotypic endpoints more strongly relate to clinical outcomes, and late changes in functional endpoints strongly relate to clinical outcomes. Future research may focus on phenotypic and functional measures as predictors, whereas research on mechanisms using biological predictors may aid intervention development.

2. Is there utility in developing a "Cancer Aging Index" analogous to the Frailty Index or the VACS Index? This might facilitate the design and assessment of clinical trials for interventions.

3. Does risk of cancer relapse or secondary malignancies correlate with physiological impact (e.g., aging hallmarks)?

4. What are the biomarkers of aging that should absolutely be included in aging cancer studies?

5. Is there a standard toolbox of hallmark measures?

6. How do we measure the rate of aging using biomarkers in a cancer context?

7. Are there useful biomarkers of aging for large cancer-survivor research populations, such as the Pace of Aging?

8. Are the measures needed to elucidate aging mechanisms different from clinical aging measures?

**Box 4** outlines research gaps in the area of biological aging markers and phenotypes in cancer survivors.

## Clinical Aging Phenotypes

### *Fitness and Frailty*

Frailty is an aging phenotype and a clinical marker of aging. It is a useful indicator because individuals are placed along a continuum, ranging from "fit" to "frail." Frailty can be used to estimate biological age and is predictive of health outcomes and mortality. The Clinical Frailty Scale is often used to assess patients' frailty in a clinical setting to appropriately provide care and determine toxicity. The Frailty Index is a multidimensional assessment of frailty risk, based on deficit accumulation. The concept of frailty should be expanded outside of geriatric populations and these indices modified to include components more applicable to younger individuals.

**Box 5** outlines research gaps in the area of clinical aging phenotypes in cancer survivors.

---

**BOX 5: CLINICAL AGING PHENOTYPES RESEARCH GAPS**

1. Is it useful to use frailty as an outcome in younger cancer survivors? What are the most important domains to include in a deficit model for this population?

2. In the cumulative deficit model, many factors can be used to create a frailty model. Is the variability different according to the factors used, even if the mean estimate is the same?

3. What other aging phenotypes, aside from frailty, should be used to assess aging in cancer survivors?

4. Do we need to know the mechanisms underlying frailty in cancer patients to adequately treat frailty or to treat the cancer?

5. What is the utility of including a frailty-type measure as part of the survivorship care plan? Would this guide recommendations for surveillance or follow-up care?

6. Is allostatic load an early indicator of frailty?

7. Is there a way to use linked data to examine frailty in cancer survivors (e.g., Surveillance, Epidemiology, and End Results (SEER) or Medicare)?

8. Does frailty status predict relapse or secondary cancers?

9. Is there a way to reduce the burden of completing a deficit accumulation scale (EHR/self-report)?

---

## Cognitive Markers of Aging

### *Cognition in Adult Survivors of Childhood Cancers*

Cross-sectional studies of adult survivors of childhood cancers have demonstrated that this population exhibits lower performance on measures of memory and processing speed. Additionally, studies have shown that this population also has reduced cortical thickness and increased Tau protein at the time of diagnosis and treatment, which is predictive of decreased processing speed and white matter integrity. Increased toxicity of cancer treatment in this population is associated with lower performance scores on measures of processing speed and memory. More research is needed to fully understand if cancer treatment presents an initial "hit" to the biological system followed by a paralleled aging trajectory with weakened reserve, or if it demonstrates an accelerated aging trajectory. Longitudinal studies with multimodal assessments, including different methods of assessing cognitive impairment, are needed to address these research gaps.

### Thinking and Living with Cancer

The purpose of the Thinking and Living with Cancer (TLC) study is to prospectively assess cognitive changes in older breast cancer survivors compared to matched cancer-free controls. The study found that comorbidity at baseline is associated with cognitive impairment, and that apolipoprotein E (APOE) 4–positive participants receiving chemotherapy (with or without hormonal treatment) experienced a decline in attention, processing speed, and executive function. Animal models of APOE3 and APOE4 younger mice suggest similar interactions with chemotherapy as seen in these initial human studies. More work is in progress to replicate these findings in older animals to more fully understand predictors of cognitive aging.

**Box 6** highlights critical research questions related to cognitive markers of aging in cancer survivors.

> **BOX 6: COGNITIVE MARKERS OF AGING RESEARCH GAPS**
>
> 1. What is the optimal (feasible) multimodal assessment of cognitive function?
>
> 2. Should current research focus on standard domains of cognitive function or on brief measures that may be best at determining slowed processing speed and increased variability? Can sequential testing assess the "tipping point" that individuals experience?
>
> 3. Why are certain areas of the brain more vulnerable to cancer treatments?
>
> 4. What biomarkers (cerebrospinal fluid [CSF] biomarkers) should be included in studies of accelerated aging to examine mechanisms of cognitive change?

## Psychosocial Markers of Aging

### Self-Perceptions of Aging

Psychosocial factors may be key effect modifiers, mediators, or perhaps even markers of the aging trajectory in cancer survivors. One potential marker is perceived age, since individuals are often good predictors of their own health status. Self-rated health has been linked to various outcomes, including physical and mental health status, preventive healthcare utilization, health behaviors, and mortality. Also, perceptions of one's own health may lead to altered health-related behavior and improve health (a feedback loop). Research into these and other psychosocial measures, such as isolation, loneliness, and social support, are important to consider as predictors, mediators, and modifiers of age-related conditions. Additionally, the ways in which aging is portrayed in popular culture and how they may impact individuals' health and wellness outcomes are not well understood.

**Box 7** outlines research gaps related to psychosocial markers of aging in cancer survivors.

> **BOX 7: PSYCHOSOCIAL MARKERS OF AGING RESEARCH GAPS**
>
> 1. Can self-perception of aging be used as a predictor of aging endpoints in cancer survivors?
>
> 2. How do psychosocial factors such as isolation, loneliness, and social support contribute to an accelerated aging trajectory? Can these be used to predict individuals at risk for accelerated aging?

## Meeting Summary

## Systems Science Approach

1. Aging and Cancer in the Context of Personal, Dense, Dynamic Data Clouds
   (Nathan Price, Ph.D.)

Multifactor, large datasets can provide unique insight into the markers of aging in cancer survivors. For example, data were leveraged from Arivale,[1] a private wellness company that collects information related to aging, wellness, and disease. Consumers can access personalized wellness information juxtaposed against the de-identified data of other consumers to get a full picture of their optimal wellness program. This collection of Personal, Dense, Dynamic Data Clouds (PD3)[2] can also be leveraged in more systematic research environments to understand predictors of health and wellness in various target populations.

Biological aging markers are "biological parameters 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."[3] The concept of biological age can be used to understand both the functional capacity of an individual at a certain time point and the change in this capacity over time. Change in functional capabilities at the system level can be a key indicator of accelerated aging following a traumatic event.

In a nine-month longitudinal study, a number of measures were collected from 100 participants, including genome sequences, 150 clinical lab tests, metabolites, proteins, gut microbiome tests, and self-tracked lifestyle and activity measures. These measures were collected in a controlled environment (e.g., timing of blood draw, testing validation), but the tests were not frequent enough to fully assess acute circumstances impacting variability, such as diurnal variation or an acute stressor. These measures were aggregated into a PD3 and overlaid with an individual's chronological age. Certain chronic conditions were associated with older biological age relative to chronological age: hypertension, Type 2 diabetes, smoking, and breast cancer. Also, certain clinical markers appear to be more strongly associated with higher biological age. If these markers are also associated with the effects of cancer or cancer treatment, this may support the observation of accelerated aging in cancer survivors.

Additionally, this type of data can be used to examine case studies of patients before and after disease transitions to look for aberrations. In one patient diagnosed with Stage 4 pancreatic cancer, blood was drawn prior to her cancer diagnosis; lab tests showed high levels of certain cancer-related proteins relative to the rest of the participants in the Arivale dataset. This same individual-level (n=1) comparison can be performed using other measures such as metabolic pathways to determine the presence or number of divergent pathways, an indication of a disease state or of aging. The purpose of this information at the individual level is to allow researchers or clinicians to better understand patients' patterns of divergence to facilitate truly personalized medicine.

2. Reliability Theory Perspective on Aging and Cancer (Leonid Gavrilov, Ph.D.)

Reliability theory is a general theory of systems failure originally developed by mathematicians, wherein failure is operationalized as an event when a required function is terminated. This could include a system or component not functioning properly anymore (a degradation failure) or the end of a system or component's life (a catastrophic or fatal failure). Using this theory, aging is defined as the increasing risk of system failure with age; non-aging is defined as the risk of failure not increasing with age. Reliability structure refers to the arrangement of components that are important for system reliability. Systems can

[1] https://www.arivale.com
[2] https://systemsbiology.org/news/2017/07/17/pioneer-100-study
[3] Baker GT 3rd, Sprott RL. Biomarkers of aging. *Exp gerontol*. 1998;23(4-5):223-239.

be connected in two major ways: 1) in series, in which the system fails when the first component fails; and 2) in parallel, in which the system fails when all components fail.

The application of the tenets of reliability theory to human biology supports a theoretical understanding of aging rate and recovery after traumatic events (e.g., cancer treatment). The human body can be considered a series-parallel system with distributed redundancy, in which vital organs are connected in series but cells within vital organs are connected in parallel. Many physiological changes that biological systems experience as part of aging can be explained by the cumulative effects of cell loss in this parallel system over time. Examples of this include atherosclerotic inflammation caused by exhaustion of progenitor cells or decline in cardiac function caused by a failure of cardiac stem cells to replace myocytes. The existence of redundancy in the human body causes the system to be tolerant to damage (without redundancy, the system would die after a single random damage) but also to accumulate damage until a threshold is reached. This damage accumulation is referred to as aging. In biological systems, there is a high level of redundancy and a high damage load. Using a mathematical failure rate can theoretically approximate a biological system's mortality.

The High Initial Damage Load (HIDL) hypothesis indicates that "adult organisms already have an exceptionally high load of initial damage, which is comparable with the amount of subsequent aging-related deterioration accumulated during the rest of the entire adult life."[4] Humans are born with some initial damage and continue to accumulate damage throughout their lives due to system redundancy. The extent of this damage is mediated by factors such as the environment, pathogens, disease, treatment for disease, and lifestyle. Extensive damage accumulation can be optimally prevented during early developmental years to postpone the effects of morbidity and mortality.

## DISCUSSION

The first part of the discussion centered on differentiating aging and death as endpoints in reliability theory. In some cases, patients have declining physical function, but death does not ensue immediately. Within the theory, this can be addressed by changing the designated "failure endpoint" of the system—if the endpoint is not death, it could also be disease state or failure of an organ system.

### *Defining Health and Disease States*

Participants then discussed how a "state of health" is defined within Dr. Price's models to allow identification of divergent measures. There are a number of ways to define this state of health or wellness. It is possible to look at a young, healthy population as a reference for health; measures that deviate from those found in that healthy population are considered atypical. It is also possible to compare individuals to groups of healthy individuals in the same age range, to control for chronological age as a factor driving variability. The definition of these states is a key question that needs to be addressed when using rich datasets for establishing health and wellness recommendations. To the same end, it is important to define what a disease is in the context of a "state of health." Does a disease state include psychosocial well-being, deviations in cognitive health, or inability to perform functional tasks?

### *Breast Cancer and Biological Age*

Participants expressed interest in Dr. Price's finding that breast cancer was associated with higher biological age relative to chronological age, because some breast cancer patients have been observed to have better survival and self-reported happiness than their counterparts without a cancer diagnosis. In Dr. Price's research, breast cancer was chosen for study as it was the most prevalent cancer in the dataset. However, the biological/chronological age relationship was quite variable over time, particularly when cancer and other confounders were involved. Dr. Price noted that this is an emerging area of research, and more work should be done to understand and account for this large variability. Some of this variability may not be due to lack

---

[4] Gavrilov LA, Gavrilova NS. Early-life programming of aging and longevity: The idea of high initial damage load (the HIDL hypothesis). *Ann NY Acad Sci.* 2004;1019(1):496-501.

of sensitivity in measurement or methodological issues; instead, it could be an early warning sign of systemic instability.

### System Science and Childhood Cancers

The discussion turned to the role of younger cancer survivors in understanding accelerated aging and the ability to detect "initial damage" or markers in young cancer survivors that could provide clues about accelerated aging trajectories. One discussant noted that there is likely a key difference in the theoretical model as it applies to childhood cancer survivors. Cancer in children may be more reliant on germline genetics (because they have not had as much time to accumulate mutations). They also likely end up with somatic damage due to the cancer treatment, which may either lead to accelerated aging or put them on a parallel trajectory of aging with a lower level of resilience. The population of childhood cancer survivors is particularly interesting because longer longitudinal follow-up periods are possible.

### Data Availability and Generalizability

Selection bias and generalizability were discussed as important methodological issues when using research driven by private, consumer data because the population characteristics are restricted to those who opt into the service and may leave out important subgroups. In this case, individuals who are older or more severely ill could be less likely to opt into a wellness program and/or less likely to consent to sharing their data.

Dr. Price recommended a number of established datasets that could be valuable sources of information for research on accelerated aging in cancer survivors:

- Alzheimer's studies, where the control participants may have a lot of valuable molecular data
- iCarbonX (Jun Wong, Ph.D., formerly with Beijing Genomics Institute)[5]
- Sema4 (Eric Schadt, Ph.D., Mount Sinai Health System)[6]
- *All of Us* (however, limited non-genomic measures)[7]
- Genomics England[8]
- UK Biobank[9]

## Clinical Markers of Aging

### 3.   Staging the Aging (Harvey Jay Cohen, M.D.)

Health assessment and intervention in older patients involves multiple, overlapping domains, including medical, physiologic, cognitive, affective, functional, resilience, economic, psychosocial, and environmental. Older patients are often treated by the same medical specialists or in the same clinical environments as younger patients, yet their health issues and treatment include key differences that are important to recognize. Older patients often undergo physiologic changes or deterioration at a more rapid speed, have a higher prevalence of disease and comorbidity, and may under-report symptoms. Due to decreased resilience to stressors and increased risk of frailty, older patients may have higher rates of adverse effects to medications and therapies, making assessment of possible toxicity an essential element of geriatric care.

Functional age clinically measures a patient's ability to perform activities of daily life and thereby characterizes health status in a way that is not solely dependent on chronological age. Among patients of the same chronological age, functional age may vary widely; this variability may be attributed to the occurrence of comorbidities, past traumatic health events (e.g., receipt of chemotherapy), or other parameters of aging. Geriatricians and researchers should systematically collect health information to

---

[5] https://www.icarbonx.com/en
[6] http://www.sema4genomics.com/ourstory
[7] https://allofus.nih.gov
[8] https://www.genomicsengland.co.uk
[9] http://www.ukbiobank.ac.uk

achieve a broader picture of the health status and vulnerability of a patient. Key parameters and ways to measure clinical health status are described in **Table 1**.

**TABLE 1: PARAMETERS OF HEALTH AND CLINICAL ASSESSMENT**

| Health Parameters | Clinical Tools for Measurement |
|---|---|
| **Physiological state, homeostasis** | ▪ Standard laboratory and physical measures<br>▪ Biological aging measures |
| **Presence or absence of chronic disease** | ▪ Medical examination and history (e.g., electronic health records) |
| **Level of physical and cognitive function** | ▪ Self-reported activities of daily living<br>▪ Physical performance measures<br>▪ Cognitive performance measures |
| **Resilience** | ▪ Ability to respond to stressors |
| **Self-rated health** | ▪ Survey questionnaires |

The Comprehensive Geriatric Assessment is "a multifaceted assessment of factors contributing to the health and well-being of complex elderly individuals." The assessment combines validated instruments and medical evaluation to systematically characterize a patient's functional status, comorbidities, cognition, nutritional status, psychosocial status, and medication status (e.g., polypharmacy). This technique has been found to predict survival and toxicity in geriatric populations.[10] The Deficit Accumulation Index (i.e., the actual number of deficits in an individual, divided by the number of potential deficits) can be derived from the constellation of measures in the Comprehensive Geriatric Assessment and used to define health, well-being, and disease status in older patients. This index has been found to be predictive of frailty, and other outcomes, like toxicity and re-hospitalization in older patients who received chemotherapy.[11]

Resilience is "the ability of an organism to appropriately respond to a stressor and return to basal physiology." The concept of resilience can be studied as a key predictor or outcome to inform aging processes in cancer survivors. Resilience may explain why some older cancer survivors return to relatively normal levels of physical function after receiving treatment, while others may experience lower or more rapidly decreasing levels. Research in this field suggests that physical resilience is mediated by an individual's health and functioning at baseline, presence and symptoms of chronic disease, type of radiation treatment, self-efficacy for physical activity, and social support.[12]

To improve researchers' and clinicians' ability to "Stage the Aging," there is a need for additional research on the applications of tools and to refine assessments, like the Comprehensive Geriatric Assessment. There is also a need for validated, sensitive, and clinically feasible measures to assess resilience in both older and younger patients at risk for accelerated aging. Finally, because data capture is derived from a wide variety of sources (e.g., electronic health records, validated instruments, self-report), effective aggregation of information is crucial for its future use and acceptability in a clinical environment.

4.    Physical Performance Measures in Aging and Cancer (Stephanie Studenski, M.D., M.P.H.)

Physical performance measures are "observed and quantitated behaviors reflecting multisystem body functions." These behaviors may be single tasks (e.g., walking a certain distance, grip strength) or a combination of multiple tasks (e.g., the Short Physical Performance Battery, involving a walk test, chair

[10] Palumbo A, Bringhen S, Mateos M-V, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. *Blood*. 2015;125(13):2068-2074.
[11] Cohen HJ, Smith D, Sun C-L, et al. Frailty as determined by a comprehensive geriatric assessment-derived deficit-accumulation index in older patients with cancer who receive chemotherapy. *Cancer*. 2016;122(24):3865-3872.
[12] Duan-Porter W, Cohen HJ, Demark-Wahnefried W, et al. Physical resilience of older cancer survivors: An emerging concept. *J Geriatr Oncol*. 2016;7(6):471-478.

rise, and tandem stands). These measures have been assessed for reliability and validity, and some are even reflected in animal models for a broad application of findings.

Physical performance measures are good predictors of future health, function, and survival. In some cases, they can better predict future outcomes (e.g., disability status) than self-report or clinical diagnosis. In particular, gait speed, although a simple and common functional measure, has been found to perform comparably to more complex predictive health models or batteries of multiple functional measures. Additionally, it accurately predicts survival, as demonstrated by a 21-year consortium analysis of more than 34,000 older adults.[13] Although the goal of walk tests is to quantify gait speed, the inability to start or complete a walk test is also an effective primary outcome in older adults. Finally, although many functional tests are burdensome and conducted cross-sectionally, longitudinal assessment is the only way to characterize within-person change and capture functional aging trajectories over time.

An emerging area of functional performance research is the concept of cognitive processing speed as an indicator of fundamental function. A decline in this measure, referred to as psychomotor slowing, may be indicative of a decline in a number of other cognitive areas, such as perception, retrieval, movement, or initiation. Tests for psychomotor slowing can be incorporated into functional batteries to achieve a more comprehensive understanding of a patient's functional status.

When considering an individual under periods of stress (e.g., cancer diagnosis or treatment), it is important to understand the risks associated with loss of physical reserve, or capacity beyond usual function. When individuals experience reduced functional capacity due to a stressor, they are less able to combat additional problems that may appear clinically during that time. This could exceed their capacity to overcome and return the system to homeostasis. Some of the loss of reserve occurs sub-clinically, where patients lose reserve but existing functional measures are not sensitive enough to detect a loss (i.e., a ceiling of detection). Sequential testing may improve the sensitivity of functional assessments. In this case, all study participants are initially tested with a low-demand task. Participants who perform at or near the ceiling of detection are given higher-demand tasks (e.g., endurance walk testing and expanded functional testing such as the Health, Aging and Body Composition Physical Performance Battery) to discriminate the limits of function. Sequential functional testing is an effective way to assess reserve and reduces participant burden.

In addition to implementing functional performance measures in the clinical setting, these tests can be used to connect biological indicators of the rate of aging to function. In mice, the transplantation of senescent cells caused reduced physical performance and decreased survival, even in younger mice.[14] Similarly, in humans, cellular senescence is associated with reduced measures of physical performance, indicating a linkage between the molecular measure of senescence and function.[15]

## DISCUSSION

### *Study Power and Depth*

Discussion immediately following Dr. Cohen's presentation focused on study design and methodological challenges associated with his approach to "staging the aging." Meeting participants were concerned that trials as they currently exist are not able to enroll enough patients with variability by cancer type, chemotherapy type, and past exposures. The group discussed initiating larger trials or designing trials for denser sampling and richer data as potential solutions, and ultimately suggested addressing this issue with preclinical models, pooled datasets, or consortia with the most common cancers (e.g., breast and prostate). Future research should identify important risk factors and aging endpoints and enroll populations with sufficient variability and statistical power.

---

[13] Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA*. 2011;305(1):50-58.

[14] Xu M, Pirtskhalava T, Farr JN, et al. Senolytics improve physical function and increase lifespan in old age. *Nat Med*. 2018;24(8):1246-1256.

[15] Justice JN, Gregory H, Tchkonia T, et al. Cellular senescence biomarker p16 INK4a + cell burden in thigh adipose is associated with poor physical function in older women. *J Gerontol A Biol Sci Med Sci*. 2018;73(7):939-945.

Challenges with power calculations were also discussed. Power calculations to determine adequate sample size are generally based on a strong, validated measure in conjunction with past, similar research to estimate effect size. However, in an emerging field with a lot of exploratory research, these components are often unavailable. More research is needed to establish universally accepted and validated measures to facilitate accurate power calculations for future studies. For the time being, this may be accomplished using adaptive study designs, where participants are recruited on a rolling basis.

### Ceilings and Floors of Detection

Following Dr. Studenski's presentation, the group discussed the utility of functional measures in geriatric assessments and aging research, as these measures often capture more complex deficits. For example, a gait speed test may be simultaneously assessing cardiopulmonary capacity, muscle strength, and balance, among other factors. A concern expressed by one participant about functional measures is their potential inability to detect impaired function or changes in function in younger, healthier patients—a "ceiling" effect. Similarly, certain functional measures may not be applicable to the oldest, non-ambulatory patients—a "floor" effect. Dr. Studenski posited that a sequential or "stepped" approach could be employed for most measures to assess a wide range of ages and also gain an understanding of physical reserve. Using this approach, all patients would be assessed using a basic measure of function. Then, those who performed at or near the ceiling could be tested again using a more difficult test. As for patients near the floor of a functional test, their inability to perform a test can itself be a valuable indicator of health. Other research domains (e.g., disability literature) may be informative of validated functional measures that would apply to non-ambulatory patients, including self-reported difficulty with daily tasks (e.g., Activities of Daily Living (ADLs) and (Instrumental Activities of Daily Living (IADLs)). For example, upper extremity tests may be a validated measure of function in non-ambulatory patients, but it is not necessarily comparable to gait speed, and therefore may not be predictive of health outcomes and mortality.

The functional performance of master athletes who are very fit over the course of their lives may be an interesting population of study, since aging contributes to peak performance levels. Most very fit people, with the exception of extreme athletes, such as those who run ultramarathons, still perform higher on geriatric indices or performance measures even with a cancer diagnosis. This suggests that they may have better recovery outcomes and potentially more resilience than their less-fit counterparts.

Functional ability may be the "tipping point," wherein individuals progress from a stable to a less functional phenotype. Thus, it is important to note that a decline in function is rarely a strictly linear process, and that the tipping point often depends on the magnitude of the stressor, as well as the individual's baseline vulnerability to stress.

### Future Research and Considerations

It was noted that a basic toolkit of validated, sequential measures for physical and cognitive function should be created to support the treatment and management of all cancer survivors. For cognition, there may be more sensitive tests outside of the standard neuropsychology batteries that can better detect subtle changes in cognitive function, particularly within the domains of processing speed, attention, or reaction time.

It was suggested that exploring the following research domains may provide insight to gain a deeper understanding of functional measures in varied populations:

- The disability literature (for functional testing in non-ambulatory people)
- The head-injury literature in children/young athletes (for cognitive testing in younger cancer survivors)
- Literature surrounding functional measures and lifetime/professional athletes (for functional testing in very fit people)

Given a number of unknowns about predictors and measures of accelerated aging, an epidemiological study was proposed to connect cancer survivors' past exposures (e.g., experience, history, resilience)

with their current and future outcomes. Is there a measure available that can accurately capture antecedent events impacting a person's probability of accelerated aging? Is this measure biological age? If so, do we have a validated way to implement it in a study setting?

Overarching questions were posed to the group:

1. Are there existing databases that can be leveraged to understand accelerated aging in cancer survivors?
   - The National Clinical Trials program
   - Cohort studies of cancer survivors funded by NCI
   - St. Jude Lifetime Cohort
   - Baltimore Longitudinal Study of Aging
   - Other research fields may have crucial insights into accelerated aging, or access to relevant data. These specialties include:
     - HIV research groups
     - Chronic obstructive pulmonary disease
     - Chronic kidney disease
     - Sepsis
2. Are there well-studied, validated measures that can be added to existing studies to elucidate aging trajectories in cancer survivors?
   - It may be possible to add additional measures to these trials to better understand antecedent events and aging. These measures should include:
     - Grip strength
     - Gait speed
     - Triar Social Stress Test
   - Should a full, systematically implemented Geriatric Assessment be added to trial protocols when feasible?

## Biological Aging Markers and Phenotypes

### 5. Time and the Metrics of Aging (Luigi Ferrucci, M.D., Ph.D.)

Although aging research often focuses on the health and well-being of individuals later in life, it is important to examine the effects of aging using a life-course approach. Investigation into younger populations—including environmental exposures, early-life health events, and predictors of disease—is an important step to understanding aging trajectories. To do this, researchers should leverage the power of longitudinal studies. This type of study attempts to control for differential lifetime environmental exposures, such as periods of economic stress or war, popularity of industrial chemicals, or discovery of new pharmaceuticals. It also deals with selective mortality, which occurs when only the healthiest individuals with the fewest chronic diseases are able to participate in the study until late in life. Observation of the oldest cohorts of individuals becomes difficult because of the high rates of multimorbidity, as participants experience increasing numbers of chronic diseases over time.

Many measures have been put forward as metrics of aging. They generally fall into three domains. The first includes functional aging, or metrics that have an impact on daily life. Functional aging includes cognitive function, physical function, mood, and mental health. Second is phenotypic aging, which refers to the impact of aging on an individual's phenotype, including indicators such as body composition, energetics, homeostatic mechanisms, and brain health. Finally, biological aging, or the root mechanisms of aging, includes molecular damage, defective repair, energy exhaustion, and signal or noise reduction. Biological aging includes an interplay between damage (e.g., accumulation of somatic mutations) and physiological compensation (e.g., DNA repair capacity). Phenotypic aging occurs when the body's compensatory mechanisms are overwhelmed by an accumulation of biological damage. Although function is often preserved even during biological and phenotypic decompensation, functional decompensation eventually occurs with the accumulation of enough damage.

The assessment of functional and phenotypic aging is essential to clinical care. However, research on the metrics of biological aging allows a deeper understanding of the mechanisms of aging, and thus leads to the development of effective interventions and prevention. Some of these biological aging metrics are briefly described as follows.

### Genomic Instability

The accumulation of somatic mutations, or increasing genomic instability, may be a key metric of biological aging. Research has demonstrated that single nucleotide variants accumulate with age, with rates of accumulation possibly varying due to an individual's exposure to a toxic environment. Similarly, genomic research indicates that the decline in human skeletal muscle function with aging may be attributed to an accumulation of somatic mutations in satellite cells.[16] Higher levels of mutations may impact the ability of these cells to facilitate skeletal muscle hypertrophy, regeneration, and remodeling, leading to reduced functional capacity.

### Epigenetics

Epigenetics is the study of changes in an organism caused by modifications to gene expression, rather than changes to the actual genetic code. In aging research, one of the most commonly studied epigenetic changes is methylation, a biochemical process wherein methyl groups bind to DNA. This accumulation of methyl groups impacts gene expression and thus effects change in the organism. DNA methylation (DNAm) levels can be used to accurately predict chronological age across all tissues and cell types throughout the human life course. This "epigenetic clock" can be modified (e.g., DNAm phenoage studied by Morgan Levine, Ph.D., at Yale University) to predict healthspan, morbidity, and mortality. The study of epigenetic accumulation can therefore be applied to aging research in cancer survivors to provide a stronger understanding of biological aging. However, a key limitation is our current inability to quantify past stressors and epigenetic modulations experienced by an individual prior to a cancer diagnosis.

### Cell Senescence

Cellular senescence refers to the "irreversible growth and proliferations arrest induced by stress," or the phenomenon by which normal cells cease to divide.[17] The accumulation of senescent cells is associated with aging and impaired regeneration of tissues. In addition, increased cellular senescence leads to cells acquiring a senescence-associated secretory phenotype (SASP), which drives the secretion of matrix proteases, pro-inflammatory cytokines, and epithelial growth factors. This pro-inflammatory environment can disrupt tissue structure and create a permissive microenvironment for cancer growth. At the molecular level, some markers of senescence (e.g., P16INK4a) have been directly associated with a loss of physical function in older adults, impacting mobility, muscle strength, and central obesity. This marker has also been found to be positively associated with elastic fiber morphology, facial wrinkling, and perceived age. Using markers of cellular senescence, including SASP proteins, is a key way to measure and contextualize biological aging.

### Mitochondrial Function

Mitochondrial function is a measure of chemical energy being created in an organism's cells, and it has been found to decline with age. This function can be measured using $^{31}$phosphocreatine ($^{31}$p) recovery time (PCr), an indicator of mitochondrial capacity in skeletal muscle. This metric of mitochondrial function links reduced skeletal muscle strength and decreased walking performance with aging, serving as a unique bridge between biological and functional aging.

---

[16] Franco I, Johansson A, Olsson K, et al. Somatic mutagenesis in satellite cells associates with human skeletal muscle aging. *Nature Commun.* 2018;9(1):800.
[17] Hayflick L. The limited in vitro lifetime of human diploid cell strains. *Exper Cell Res.* 1965;37(3):614-636.

6.    Aging Associated Cancers—Not So Inevitable (James DeGregori, Ph.D.)

The current paradigm describing aging-related consequences of cancer is that cancer incidence is limited by the occurrence and accumulation of oncogenic mutations. However, different cancer types demonstrate similar aging-dependent incidence, regardless of their different driver mutations and organized stem cell pools. This observed age dependence is the basis for a modified paradigm of cancer incidence. Although there are strong mechanisms for tumor suppression during developmental and reproductive years, there is minimal natural selection against cancer beyond those reproductive years, when human ancestors would likely have already died from other causes. Cancers occurring in young people (e.g., childhood leukemias, testicular, or lymphoma) may be explained by modern lifestyles in developed nations, exposure to pathogens, or a rare event.

The Adaptive Oncogenesis Hypothesis posits that cancer incidence is based on aging and exposure-related changes to the tissue microenvironment, allowing cells with cancer-causing mutations to expand. These exposures may include factors such as smoking, radiation, diet, and endogenous microenvironmental changes (e.g. inflammation) associated with aging. In young, healthy people, stem cell fitness is high, and there are strong opposing factors to somatic evolution, thus selecting against the proliferation of cells with cancer-causing mutations. However, in older populations with accumulated exposures, the old or damaged stem cell pool is no longer optimized to the old/damaged tissue microenvironment. In this case, selective pressures against pre-cancerous cells are reduced, and the microenvironment is more favorable to the growth of cancer-causing cells (with oncogenic mutations adaptive to the altered microenvironment). Thus, the incidence of cancer depends not solely on the existence of harmful mutations but also on context-dependent preferential selection of mutated cells. In all, cancer is shaped by the changing age-dependent balance of drift, stabilizing selection, and positive selection.

An example of this age-dependent effect is seen in lung cancer, which has a strong association with old age. Older lungs generally have reduced vital capacity, weakened breathing muscles, increased fibrosis, increased presence of immune infiltrates, and increased inflammatory cytokines. EML4-ALK gene fusions (oncogenes) are more common in lung cancers of never-smokers, presenting an opportunity to study the effect of lung age and microenvironment on clonal expansions in animal models. Young and old mice were genetically modified using the CRISPR/Cas9 system such that a small fraction of lung cells contained EML4-ALK, and EML4-ALK clonal expansions were quantified. More and larger clonal expansions, leading to adenomas, were observed in older mouse lungs relative to younger lungs. Using transgenic mouse models, the expression of α1-anti-trypsin (AAT) was found to block inflammation and thus prevent the expansion of adenoma-like lesions in the aged lungs, coinciding with the reversion of a subset of aging-related changes. This observation suggests that manipulation of the microenvironment (e.g., with AAT) can modulate the fitness effects of cancer-associated mutations. While we cannot avoid most oncogenic mutations that occur during life, these studies indicate that we can alter the ability of these mutations to contribute to malignancies.

7.    Quantification of Biological Aging: Approaches to Validation (Daniel W. Belsky, Ph.D.)

Biological aging is the gradual and progressive decline of system integrity, arising from an accumulation of cellular- or molecular-level changes that ultimately lead to systemic damage. Based on this definition, exposures that accumulate from early life can lead to damage and ultimately impact aging outcomes (e.g., disease, frailty) toward the end of life. For this reason, the group agreed it was important to examine aging over the life course rather than a finite event in late life. However, the study of geroprotectors (interventions or pharmaceuticals potentially associated with slowing the rate of aging) in young and midlife humans can be difficult, since longitudinal investigation until disability or death involves research over many decades. This research can be costly and time-consuming, thus limiting the size and power of potential studies.

An alternative approach is to study the effects of geroprotectors by using measures of aging processes as surrogate endpoints, rather than using disability/mortality. However, measuring aging processes requires quantification of biological aging. Some measures of biological aging already exist, including telomere shortness, several epigenetic clocks (e.g. 353-CpG Clock, 99-CpG Clock, 71-CpG Clock), and composite indices based on clinical markers, such as KDM biological aging, and homeostatic dysregulation. However, these measures of aging are cross-sectional, compare a target individual to a reference population, and require validation. An approach to guide measuring and validating biological aging metrics is outlined in **Table 2**. One additional proposed metric of aging rate is the "Pace of Aging," which is a composite of 18 repeated measures of system integrity. This measure is associated with aging endpoints, such as balance, grip strength, motor coordination, physical limitations, cognitive decline, self-reported health, and facial aging. Additionally, the Pace of Aging has been validated based on known risk factors for age-related disability/mortality (e.g., familial longevity, childhood socioeconomic status).

**Table 2. Measuring and Validating Biological Rates of Aging**

|  | Current Standard | Problem/Challenge | Proposed Solution |
|---|---|---|---|
| **Measurement** | Measures of aging are cross-sectional, focus on accumulated differences. | Current measures do not distinguish early-emerging differences from age-related decline. | Use longitudinal, repeated measures, focusing on ongoing change within a person. |
| **Validation** | Validation criteria for biological aging metrics are that they correlate with chronological age, correlate with disease status, can forecast mortality. | Current approach to validation risks bias for mortality selection and focuses on the oldest population segment. | Use function and functional decline to validate measures. Focus on lifetime risks known to accelerate aging. |

DISCUSSION

*Adaptive Oncogenesis and Prevention*

Initial discussion centered the Adaptive Oncogenesis Hypothesis and the possibilities for prevention. Healthy lifestyle choices starting in youth may reduce the rate of aging by decreasing the rate at which tissue microenvironments become hospitable to pre-cancerous cells. Some research exists on the impact of physical activity and diet (including caloric restriction) on aging outcomes; however, more longitudinal studies are needed to fully understand the life-course effects of these factors in humans. The group also discussed how this hypothesis applies to clinical care. Maintenance of the system's microenvironment is crucial for preventing cancer relapse or toxicity. For example, chemotherapy in older cancer patients damages the tissue microenvironment, creating a more hospitable context for cancer-causing cells to rebound and become untreatable. These drugs, shown by Campisi and others, also promote cellular senescence, changing the environment further. Ideal cancer therapies would attack cancer cells and simultaneously boost the tissue microenvironment. More careful consideration of the "tissue landscape" in a clinical setting is key to improving patient outcomes.

*Functional Measures of Early Aging*

Functional ability is often the last to go, as systems can adapt physiologically so that function is retained. Therefore, aberrations in biological and phenotypic aging metrics are often seen prior to any observed functional decline. Understanding how functional performance measures can be leveraged to detect early systemic changes and assess accelerated aging are an important next step. Discerning whether all cancer patients should be assessed for markers of accelerated aging or if a risk stratified approach is suitable requires further attention. Moreover, it was noted that if molecular, phenotypic, and functional measures are continuously observed in isolation, the opportunity to disentangle the interrelationships of

these variables becomes lost. Focus on longitudinal study with multimodal measures may elucidate their complex interplay over time.

### Recommendations for Biological Markers of Aging

At numerous points throughout the meeting, the group discussed the 2013 paper *"The Hallmarks of Aging,"* which describes nine potential hallmarks of aging in different organisms, particularly mammals.[18] Some meeting participants were concerned that the findings of the paper originated from a mixture of preclinical animal models and human trials. However, the paper provides a foundation to assess if any biomarkers are ready for implementation into large-scale research and clinical studies. One think tank participant posited that the evidence base for mitochondrial function and aging is strong. For many of the other markers, however, a high degree of variability in the measures makes it difficult to observe changes with enough sensitivity to make recommendations at this time.

## Clinical Aging Phenotypes

### 8.    Frailty and Its Clinical Application (Olga Theou, Ph.D.)

In general, frailty arises when physiological reserve capacity falls below the level required to sustain homeostasis to meet the demands of everyday life. The frailty phenotype is generally considered to have three or more of the following characteristics: weight loss, mobility impairment, low muscle strength, fatigue, and low physical activity level. As pertains to overall function, frailer older adults are vulnerable to physiological and psychological stressors that may not similarly impact less-frail individuals of the same chronological age. Although frailty is often associated with older adults and poor health, it can be considered one end of the health continuum, with fitness at the opposite end. Frailty has been associated with multiple adverse health outcomes, ranging from mobility impairment to hospitalization and death. As with other aging-related concepts, frailty can be viewed as deficit accumulation, with more severely frail individuals experiencing higher levels of system deficits.

Because frailty is not solely dependent on an individual's chronological age and can be more indicative of their health and wellness status, it can be used to estimate biological age. In a clinical setting, measurement of frailty can be particularly important because geriatric patients often have multiple health problems. Currently, subjective assessments of frailty are routinely performed in these settings, but they are not always reliable or systematic. Frail individuals need to be considered differently in a clinical sense because they are less able to withstand toxic or invasive interventions and less able to tolerate polypharmacy.

The Clinical Frailty Scale is a tool that helps classify individuals on a spectrum ranging from "very fit" to "terminally ill." The deficit accumulation approach is an alternative assessment with flexibility as to the number and type of variables used. In general, the index is calculated as the number of deficits in an individual divided by the total number of deficits measured. An example of this is the 46-item Frailty Index used by the National Health and Nutrition Examination Survey (NHANES), which includes comorbidity, chronic disease, and functional and psychosocial measures. Using this index, NHANES participants with a non-skin cancer diagnosis had significantly higher frailty than participants with no cancer diagnosis. When frailty was used as an outcome, it was found that participants with a non-skin cancer diagnosis had 1.69 times the odds of being frail compared to their counterparts with no cancer. Looking at mortality, participants with a frailty index of 0.3 or greater had mortality rate 5.84 times higher than participants with a frailty index less than 0.1.

The treatment of at-risk and frail patients is a growing area of research. Interventions may be conducted in multiple domains (e.g., nutrition, medication management), particularly relating to physical activity. It is also recommended that a comprehensive assessment of at-risk or already frail patients be conducted to

---

[18] López-Otín C, Blasco MA, Partridge L, Serrano M, & Kroemer G. The hallmarks of aging. *Cell.* 2013;153(6):1194-1217.

characterize vulnerabilities and track changes over time. There is a limited consensus about the optimal components to include in a geriatric assessment. There is agreement, however, that any such assessment should lead to recommendations for pre-habilitation and prevention, support shared pre-operative decision-making and post-operative plans, and take into account clinical feasibility.

In the context of cancer survivors, future research should include use of the frailty index to better understand aging trajectories. Validated frailty assessments should be incorporated into clinical practice, including oncology. Including cancer survivors at varying levels of frailty in randomized controlled trials will capture a more representative picture of their aging trajectories. These trials could include the implementation of modified treatment plans based on frailty levels, as well as the use of frailty as a trial outcome.

## DISCUSSION

### *Frailty in Younger Populations*

Some of the discussion centered on the applicability of frailty in certain populations, and in particular on discerning whether frailty measures are sensitive enough to detect changes in relatively healthy populations of younger cancer survivors. This challenge can be addressed by looking at change in frailty over time, rather than solely cross-sectional measures. Additionally, the frailty index should be modified to exclude items that do not uniquely apply to certain populations. For example, a frailty index heavily based on the presence of comorbidities may not be informative in a younger population. There has been discussion around renaming the frailty index the "health index" because frailty as a concept is strongly associated with geriatric populations. More research is needed in middle-aged (40 to 50 years) cancer survivors to gain a deeper understanding of "pre-frail" characteristics and the optimal ways to intervene. One way to do this may be to use public data (e.g., the Medicaid Frailty Index) along with cohorts to follow cancer survivors longitudinally.

### *Applying Frailty in Clinical Care*

Much of the discussion also focused on applicability and feasibility of frailty assessment in clinical care. Some indices, including the Deficit Accumulation Index, must be completed by a clinician, which can be time-consuming and therefore not systematically performed in an active clinical setting. Dr. Theou described her work creating a pictorial Frailty Scale, so that patients would be able to self-report functional ability. Also, some functional measures can be performed by nurses or medical assistants, and select information may already be available for patients in electronic medical records. Dr. Theou also compared the use of the Frailty Scale with the Deficit Accumulation Index. The frailty scale requires measures in five specific domains (as described previously); any modification in these domains has a significant impact on the interpretation of the results. The Deficit Accumulation Index is generally composed of 30 or more items, which should be representative of multiple domains but can be modified with less of an impact to its predictive abilities. It is possible to implement both measures in a clinical setting for a full picture of a patient's frailty because many measures overlap or are easy to assess.

In a clinical setting, frailty assessments could be implemented as part of a cancer survivorship plan to get an accurate picture of a survivor at baseline and allow for recommendations as to the survivor's future health and well-being. For example, it is possible that higher frailty levels are predictive of cancer relapse because survivors may have weaker immune systems and more comorbidities. Also, frailty could potentially provide some insight into secondary malignancies in cancer survivors after they receive treatment. Frailty is a factor that is known to be strongly predictive of a number of clinical outcomes, and assessments are already being implemented in certain settings (e.g., pre-surgical cardiac patients). The crucial next step for this field is to understand how to prevent frailty and effectively intervene in frail populations.

## Cognitive Markers of Aging

### 9.  Cognitive Aging in Adult Survivors of Childhood Cancer (Kevin Krull, Ph.D.)

One of the determinants of cognitive decline is referred to as cognitive reserve, or the amount of "buffer" between the highest attained level of function and the lowest threshold of cognitive decline and dementia. Cognitive reserve allows for a certain level of protection and recovery from trauma throughout the life span. It is determined by multiple interrelated factors, which include domains such as cognitive function, life habits, life events, and brain structure. Different cognitive functions (e.g., executive functioning, memory) may have varying levels of cognitive reserve within a single individual. Also, some of these functions may be more resistant to the negative effects of aging—for example, crystalized intelligence is seen as being resistant, while fluid intelligence is not. Cognitive reserve may be impacted as a result of childhood cancer and treatment because these stressors often occur during development, before children have reached their full cognitive potential. This impact to cognitive reserve could affect an individual's trajectory of aging throughout the life course.

The purpose of the St. Jude Lifetime Cohort is to establish a lifetime cohort of childhood cancer survivors and facilitate clinical longitudinal evaluation of health outcomes in aging adults surviving pediatric cancer. In 650 adult survivors of childhood acute lymphoblastic leukemia (ALL), the highest levels of impairment (more than 50% of the sample) were seen in the domains of memory, processing speed, and executive functioning.[19] Risk for attention problems and executive function impairment increased with time from cancer diagnosis at a faster trajectory for participants who received higher doses of cranial radiation. In longitudinal analysis, about half of the 102 adults assessed since childhood showed no decline in verbal IQ over time, while the other half showed a decline of about 20 points from baseline to follow-up (mean of 27 years).[20] A comparison of adolescents and adults in the cohort who received similar ALL treatment at the time of diagnosis shows that memory problems and slow processing speed are almost twice as frequent in the adult survivors as they are in the adolescents, suggesting that these skills may be prone to rapid decline. Differences may also be seen in physiological measures such as thinning of the cerebral cortex and smaller hippocampal volume.

A number of research gaps have been identified in the area of cognitive function and childhood cancer. These include investigation into the decline in fluid abilities and functional independence during long-term survivorship, progressive loss of brain volume, and persistence of neuropathophysiology into adulthood.

More research is also needed on genetic predictors of cognitive outcomes and the potential for intervention and treatment of these outcomes. To address these research gaps, more prospective longitudinal studies are necessary to examine the change in cognitive, behavioral, and biological factors over the course of survivorship. These studies should include multimodal assessment, such as neurocognitive testing, brain imaging, serum, and CSF biomarkers.

### 10.  The TLC Study: Cognitive Aging of Older Breast Cancer Survivors (Jeanne Mandelblatt, M.D., M.P.H.)

The purpose of the Thinking and Living with Cancer (TLC) study is to assess older breast cancer survivors longitudinally and compare findings with matched non-cancer controls. Participants were assessed at three time-points (pre-treatment, 12 months, and 48 months) using objective and subjective measures of cognition. Overall, breast cancer and associated treatment seemed to accelerate cognitive aging processes. In particular, participants who were positive for the gene APOE4 receiving chemotherapy (with or without hormonal treatment) experienced a steep decline in attention, processing speed, and executive function over the course of the study.

---

[19] Krull KR, Brinkman TM, Chenghong L, et al. Neurocognitive outcomes decades after treatment for childhood acute lymphoblastic leukemia: A report from the St Jude lifetime cohort study. *J Clin Oncol.* 2013;31(35):4407-4415.
[20] Krull KR, Zhang N, Santucci A, et al. Long-term decline in intelligence among adult survivors of childhood acute lymphoblastic leukemia treated with cranial radiation. *Blood.* 2013; 122(4):550-553.

The study also connected cognitive functioning to functional well-being using the FACT Functional Well-Being Score. Participants receiving chemotherapy had consistently lower FACT scores compared to controls, while those receiving hormonal treatment had increasing scores until 24 months after study enrollment. These trajectories of functional well-being were significantly associated with self-reported cognition scores over time. Because control participants were not surgical patients, it is possible that some of the effects seen could be due to the effects of surgery on cognition. However, it is difficult to assess cognitive data prior to a surgery event, as it is unlikely to be representative of a patient's actual baseline state.

Additional research is being done using pooled data from the TLC study, the COG AGE study, and the NCI Community Oncology Research Program, allowing for increased study power. Pooling data in this way also allows for more variability between cancer phenotypes and treatment regimens and provides more opportunities for comparison. Preclinical models are also being used to further understand the findings from the TLC study. Animal models can help to elucidate the interaction between genetics and cancer treatment as they relate to cognitive impairment. For example, mice homozygous for the APOE4 allele who are also treated with doxorubicin demonstrated lower performance over time in a spatial learning and memory test, compared to APOE4 mice without treatment as well as mice homozygous for the APOE3 allele.

## DISCUSSION

### Cognition, Cancer, and Dementia

Participants discussed potential reasons for the apparent inverse relationship between cancer incidence and dementia based on demographic data. Ascertainment bias may be at play, in that patients don't receive a cancer diagnosis as frequently if they have late-stage dementia. It may also be an issue of survival bias, in that individuals are more likely to die before being diagnosed with dementia and cancer. Finally, because the coincidence of the two diseases is relatively rare, large studies would be needed to understand the apparent association.

### Participant Burden

A challenge with many cognitive assessments is that they can be lengthy and may be a burden on the patient/study participant. Shorter cognitive batteries are available that collect similar information in a shorter period of time (approximately 20 minutes). However, Dr. Mandelblatt indicated that many participants feel stressed about the assessment itself, rather than the time to completion. For example, many participants report nervousness or embarrassment if they provide an "incorrect" answer. The limitation with reducing the amount of items in the cognitive battery is that it becomes increasingly less sensitive to detecting small changes or differences in function. As with functional performance measures, a sequential approach can be taken with cognitive assessments to address participant burden as well as ceilings and floors in sensitivity.

### Comorbidities and Confounders

Currently, many cognitive function and aging studies exclude participants with vulnerabilities, such as traumatic brain injuries, anxiety, depression, or attention deficit hyperactivity disorder. However, a life course perspective suggests that these vulnerabilities need to be taken into account. It is possible that current studies are "too pure" due to restrictive eligibility criteria, and are, therefore, missing important predictors of accelerated aging. These vulnerabilities could have important interactions with factors such as psychosocial problems or health disparities, which must be taken into consideration. Another factor that may not be appropriately measured is chronic life stress, a predictor of chronic disease and poor health outcomes. More research should be done to find a validated tool to characterize chronic stress in these populations.

Finally, throughout this and other discussions, the impact of personality type on cognition and other outcomes was raised. There is some thought that certain personality types (e.g., optimistic, resilient, neurotic, conscientious) may mediate an individual's reaction to and recovery from situations of stress. More research needs to be done on the true impact of personality type on physical, cognitive, and other outcomes related to aging in cancer survivors.

## Psychosocial Measures of Aging

### 11.    The Link between Self-Perceptions of Aging and Health (Erwin Tan, M.D.)

Dr. Tan described the initiative within AARP (formerly known as the American Association for Retired Persons) to disrupt notions of aging by "challenging outdated beliefs about what it means to age," and to create opportunities for older adults to determine their own trajectory of aging. Part of this movement includes changing the way society perceives older adults and how older adults perceive themselves. Self-perceptions of aging have been linked through research to physical and mental health outcomes, preventive health care utilization rates, and mortality. Individuals with positive self-perceptions of aging tend to practice more preventive health behaviors, such as diet, exercise, and medication adherence. They are also more likely to receive cholesterol tests, mammograms, pap smears, and prostate exams. Self-perceptions of aging may mediate health and behavior outcomes through a number of causal pathways, including the fact that individuals are often good predictors of their own health. Also, perceptions of one's own health may lead to changes in health-related behavior and therefore better health (a feedback loop).

Stereotype threat is another reason why self-perception of aging may impact an individual's health and well-being status. This occurs when environmental cues (e.g., media) assert negative stereotypes about an individual's group status (e.g., older people), triggering detrimental physiological and psychological processes. Absorbed stereotypes about older people can impact key aging outcomes such as an individual's functional abilities and memory performance.

Research into these and other psychosocial measures is important when looking at the aging trajectories of cancer survivors. This research may include partnerships with AARP or private partnership with industry.

### DISCUSSION

#### *Self-Reported Health*

Some discussion following Dr. Tan's presentation focused on disentangling self-perceptions of aging and self-reported health as predictors of health and behavioral outcomes. Many studies of self-perceptions of aging did not control for self-reported health, which is known to be associated with outcomes such as morbidity and mortality. Are individuals who identify as being in good health more likely to have positive perceptions of aging? However, it is possible that humans' ability to sense their own health status runs deeper than self-reported health. This is demonstrated by the power of asking patients "How do you feel?" in a clinical setting. Often, patients may begin to report non-specific negative feelings prior to a traumatic health event, while early systemic disturbances are beginning to manifest. These findings could be further developed with more robust studies or by adding measures of self-perceptions of aging to established cohorts.

#### *AARP Initiatives*

The group discussed current advocacy initiatives at AARP to support older adults' positive perceptions of aging. These initiatives include a journalism fellowship to improve communication surrounding the lives of older adults, and efforts to connect with outdoor retailers to improve imagery of older adults in their marketing materials. Some meeting participants were concerned that such marketing initiatives may unintentionally create unrealistic expectations for older adults who are not fit and healthy. Seeing imagery

of the positive effects of aging could cause them to feel ashamed of their own health status, which could lead to negative consequences.

***Psychosocial Predictors of Disease***

Although there are many psychosocial measures available, some may be more predictive of disease risk than others. Some of these measures include isolation and loneliness, as well as measures of a resilient personality or positive ways of dealing with stressful situations. Finally, social support has long been known to be a predictor of positive outcomes, particularly in the case of cancer survivors. Social support is having not only available friends or family but also people to talk to or feel emotionally supported by.

## Final Discussion

The discussion concluded with some remaining points. One think tank participant noted that a dialogue about sexual function is often missing, but this type of function is often highly linked to a cancer survivor's self-reported physical and mental health. Cancer survivors frequently report feeling as if they are "outrunning their bodies." Understanding the mechanisms and appropriate measures to capture the underlying phenomena that give rise to these feelings is paramount to providing tangible strategies to mitigate or remediate the effects of cancer and its treatment and optimize successful aging in this population.

## Appendix A: Think Tank Agenda

**NIH › NATIONAL CANCER INSTITUTE**

**Division of Cancer Control and Population Sciences**

**Cancer & Accelerated Aging** ADVANCING RESEARCH FOR HEALTHIER SURVIVORS

**Measuring Aging And Identifying Aging Phenotypes In Cancer Survivors**

| | | |
|---|---|---|
| **Wednesday, July 25, 2018**<br>National Cancer Institute, Shady Grove Campus<br>Seminar Room 406/Joseph F. Fraumeni<br>9609 Medical Center Drive<br>Rockville, MD 20850 | | |
| **12:00-12:30 PM** | *LUNCH — All attendees are responsible for their own food and beverages. Boxed lunches are available for $13; they must be ordered at the time of registration and paid for in cash at check-in.* | |
| 12:30-12:35 PM | **Welcome and Introductions** | Paige Green<br>Lisa Gallicchio<br>Andy Burnett |
| 12:35-12:45 PM | **Perspectives from the NCI Office of Cancer Survivorship** | Deborah K. Mayer |
| 12:45-12:50 PM | **Overview of Think Tank Goals** | Arti Hurria<br>Jennifer Schrack |
| 12:50-12:55 PM | **Systems Science Approach** | Paige Green |
| 12:55-1:25 PM | **Aging and Cancers in the Context of Personal, Dense, Dynamic, Data Clouds** | Nathan Price |
| 1:25-1:30 PM | Q&A | |
| 1:30-1:50 PM | **Reliability Theory Perspective on Aging and Cancer** | Leonid Gavrilov<br>Natalia Gavrilova |
| 1:50-1:55 PM | Q&A | |
| 1:55-2:15 PM | Discussion | Facilitated by Paige Green |
| 2:15-2:30 PM | **Summary of Discussion and Next Steps** | Paige Green |
| **2:30-2:45 PM** | **BREAK** | |

| | | |
|---|---|---|
| 2:45-2:50 PM | **Clinical Markers of Aging** | Jennifer Schrack |
| 2:50-3:10 PM | **Staging the "Aging"** | Harvey Cohen |
| 3:10-3:15 PM | *Q&A* | |
| 3:15-3:35 PM | **Physical Performance Measures in Aging and Cancer** | Stephanie Studenski |
| 3:35-3:40 PM | *Q&A* | |
| 3:40-4:00 PM | **Discussion** | Facilitated by Jennifer Schrack |
| 4:00-4:15 PM | **Summary of Discussion and Next Steps** | Jennifer Schrack |
| 4:15-4:30 PM | **Day 1 Wrap-Up** | Arti Hurria<br>Jennifer Schrack |
| ***5:30-7:00 PM*** | ***Optional Happy Hour*** *— All attendees are responsible for their own food and beverages.*<br>Fontina Grille<br>801 Pleasant Drive<br>Rockville, MD 20850<br>(301) 947-5400<br>Reservation is under Julie Collier. | |

| | Thursday, July 26, 2018<br>Johns Hopkins University<br>Room 307<br>9601 Medical Center Drive<br>Rockville, MD 20850 | |
|---|---|---|
| 8:30-8:45 AM | Welcome and Day 1 Recap | Arti Hurria<br>Jennifer Schrack |
| 8:45-8:50 AM | **Biological Aging Markers/Phenotypes** | Judith Campisi<br>Russell Tracy |
| 8:50-9:20 AM | Time and the Metrics of Aging | Luigi Ferrucci |
| 9:20-9:25 AM | Q&A | |
| 9:25-9:45 AM | Aging-Associated Cancers – Not So Inevitable | James DeGregori |
| 9:45-9:50 AM | Q&A | |
| 9:50-10:10 AM | Quantification of Biological Aging:<br>Approaches to Validation | Daniel Belsky |
| 10:10-10:15 AM | Q&A | |
| 10:15-10:35 AM | Discussion | Facilitated by Judith Campisi<br>and Russell Tracy |
| 10:35-10:50 AM | Summary of Discussion and Next Steps | Judith Campisi<br>Russell Tracy |
| 10:50-11:05 AM | *BREAK* | |
| 11:05-11:10 AM | **Clinical Aging Phenotypes** | Kirsten Ness |
| 11:10-11:30 AM | Frailty and Its Clinical Application | Olga Theou |
| 11:30-11:35 AM | Q&A | |
| 11:35-11:55 AM | Discussion | Facilitated by Kirsten Ness |
| 11:55-12:10 PM | Summary of Discussion and Next Steps | Kirsten Ness |
| 12:10-1:10 PM | *LUNCH — All attendees are responsible for their own food and beverages.* | |
| 1:10-1:15 PM | **Cognitive Markers of Aging** | Tim Ahles |
| 1:15-1:35 PM | Cognitive Aging in Adult Survivors of<br>Childhood Cancer | Kevin Krull |
| 1:35-1:40 PM | Q&A | |
| 1:40-2:00 PM | The Thinking and Living with Cancer (TLC)<br>Study: Cognitive Aging of Older Breast<br>Cancer Survivors | Jeanne Mandelblatt |
| 2:00-2:05 PM | Q&A | |
| 2:05-2:25 PM | Discussion | Facilitated by Tim Ahles |
| 2:25-2:40 PM | Summary of Discussion and Next Steps | Tim Ahles |
| 2:40-2:55 PM | *BREAK* | |

| | | |
|---|---|---|
| 2:55-3:05 PM | Psychosocial Markers of Aging | Paige Green |
| 3:05-3:25 PM | The Link Between Self-Perceptions of Aging and Health | Erwin Tan |
| 3:25-3:30 PM | Q&A | |
| 3:30-3:50 PM | Discussion | Facilitated by Paige Green |
| 3:50-4:00 PM | Summary of Discussion and Next Steps | Paige Green |
| 4:00-5:00 PM | Day 2 Summary, Wrap-Up, and Next Steps | Arti Hurria<br>Jennifer Schrack |
| 5:00 PM | ADJOURN | |

**NIH › NATIONAL CANCER INSTITUTE**

**Division of Cancer Control and Population Sciences**

**Cancer & Accelerated Aging** ADVANCING RESEARCH FOR HEALTHIER SURVIVORS

## Scientific Steering Committee And Invited Speaker Biographies

## Scientific Steering Committee

### Tim Ahles, Ph.D.

Dr. Tim Ahles received his Ph.D. (1982) in Clinical Psychology from the State University of New York at Albany and completed his internship at the University of Mississippi Medical Center. While on faculty of the Department of Psychiatry of Dartmouth Medical School he developed and directed the Center for Psycho-Oncology Research (1992-2006), which focused on quality of life and symptom management research in cancer patients. In April 2006, he moved to Memorial Sloan Kettering Cancer Center to develop and direct the Neurocognitive Research Laboratory.

Over the last 25 years, his research has focused on cognitive side effects of chemotherapy in patients with breast cancer and lymphoma. These studies have included cross-sectional and longitudinal studies of chemotherapy-induced cognitive change utilizing neuropsychological assessments and structural and functional MRI, examination of genetic factors and biomarkers that increase risk for cognitive changes, study of the interface of treatment-induced cognitive change and aging, the evaluation of cognitive behavioral interventions, and collaborative translational animal model studies designed to identify mechanisms of chemotherapy-induced cognitive change.

### Andy Burnett, M.S.

Andy Burnett is CEO of Knowinnovation, a company dedicated to accelerating scientific research through the application of the theory and practice of deliberate creativity.

### Judith Campisi, Ph.D.

Dr. Judith Campisi received a Ph.D. in Biochemistry from the State University of New York at Stony Brook, and postdoctoral training in cell cycle regulation at the Dana-Farber Cancer Institute and Harvard Medical School. As an Assistant Professor at the Boston University Medical School, she studied the role of cellular senescence in suppressing cancer, and soon became convinced that senescent cells also contributed to aging. She left Boston University as an Associate Professor to become a Senior Scientist at the Lawrence Berkeley National

Laboratory in 1991. In 2002, she started a second laboratory at the Buck Institute for Research on Aging, where she is a Professor. At both institutions, Dr. Campisi established a broad program to understand the relationship between aging and age-related disease, with an emphasis on the interface between cancer and aging. Her laboratory made several pioneering discoveries in these areas, and her research continues to challenge and alter existing paradigms. In recognition of her research and leadership, Dr. Campisi received numerous awards, including two MERIT awards from the National Institute on Aging, awards from the AlliedSignal Corporation, Gerontological Society of America and American Federation for Aging Research, the Longevity prize from the IPSEN Foundation, Bennett Cohen award from the University of Michigan, Schober award from Halle University and the first international Olav Thon Foundation prize. She is an elected fellow of the American Association for the Advancement of Science and serves on numerous national and international editorial and scientific advisory boards.

### Rebecca Fuldner, Ph.D.

Dr. Rebecca Fuldner is a cellular and molecular biologist. She received her undergraduate degree in Biochemistry from the University of California, Berkeley, and a Ph.D. from the University of Wisconsin in Madison, Wisconsin. After spending five years as a senior staff fellow studying T cell activation in the Laboratory of Tumor Immunology and Biology at the National Cancer Institute, she joined The Institute for Genomic Research (TIGR) in Rockville, Maryland, and became familiar with various genomic approaches for gene discovery. The most challenging project she encountered while at TIGR was related to candidate gene identification for early onset Alzheimer's disease. In 1999, Dr. Fuldner returned to the National Institutes of Health (NIH), and she is currently the branch chief of the Aging Physiology Program within the Division of Aging Biology at the National Institute on Aging at NIH. Her portfolio includes research related to understanding the basis for senescence of the immune system in older individuals and therefore includes studies on the function of both the innate and adaptive immune systems in the elderly. In addition, her portfolio includes studies on vaccine effectiveness in elderly adults.

### Lisa Gallicchio, Ph.D.

Dr. Lisa Gallicchio is a Program Director in the Clinical and Translational Epidemiology Branch (CTEB) of the Epidemiology and Genomics Research Program (EGRP) at the National Cancer Institute (NCI). She is involved in research efforts to identify clinical and genomic factors that influence cancer treatment outcomes, including those factors that may contribute to observed disparities in health outcomes.

Prior to joining EGRP, Dr. Gallicchio was a Senior Epidemiologist in The Prevention and Research Center in the Weinberg Center for Women's Health & Medicine at Mercy Medical Center. During this time, she also served as an Adjunct Assistant Professor in the University of Maryland at Baltimore Department of Epidemiology and Public Health and the Johns Hopkins University Bloomberg School of Public Health Department of Epidemiology.

Dr. Gallicchio's work at Mercy Medical Center involved overseeing studies aimed at better understanding long-term health outcomes of cancer survivors as well as factors associated with cancer treatment adherence. She was the Principal Investigator of a cohort study

examining racial differences in the cardiovascular health effects of aromatase inhibitors, a hormonal therapy commonly used among breast cancer patients. Dr. Gallicchio's research specialties also include clarifying factors that underlie the conditions affecting the health of women during midlife. She has a particular interest in health disparities.

### Paige A. Green, Ph.D., M.P.H., F.A.B.M.R.

Dr. Paige A. Green, Ph.D., M.P.H., F.A.B.M.R., is chief of the Basic Biobehavioral and Psychological Sciences Branch in the Behavioral Research Program, Division of Cancer Control and Population Sciences, at the National Cancer Institute (NCI). Dr. Green has cultivated a biobehavioral research portfolio that focuses on elucidating biological mechanisms of psychosocial effects on health and disease. Dr. Green received her undergraduate degree in Psychology and her doctorate in Clinical Psychology from the University of Miami in Coral Gables, Florida. Her doctoral training included an emphasis on behavioral medicine and psychophysiology within the context of cardiovascular disease. Dr. Green completed her clinical psychology internship, with specialization in health psychology, at the Brown University Clinical Psychology Internship Consortium and postdoctoral fellowships at the Memorial Sloan Kettering Cancer Center and the Howard University Cancer Center. In 2005, she received a Master of Public Health degree from Bloomberg School of Public Health at Johns Hopkins University. She is an elected fellow of the Academy of Behavioral Medicine Research, a member and past leader of the American Psychosomatic Society, and program chair of the NCI Network on Biobehavioral Pathways in Cancer.

Dr. Green is a 2010 graduate of the NCI Senior Executive Enrichment & Development Leadership Program. She has received National Institutes of Health (NIH) Awards of Merit for outstanding coordination, leadership, and dedication to the NIH Genes, Environment and Health Initiative (2012) and for exceptional leadership of research advances in basic behavioral science at the NCI and NIH (2013). Dr. Green received the 2015 NIH Director's Award for exemplary performance while demonstrating significant leadership, skill, and ability in serving as a mentor, and she received the 2015 NCI Knowledge Management Program Exceptional Mentor Award. In 2015 Dr. Green was selected as one of five other federal servants to receive the 2015 Meritorious Research Service Commendation from the American Psychological Association Board of Scientific Affairs in recognition of her outstanding contributions to psychological science at the NCI.

### Jennifer Guida, Ph.D., M.P.H.

Dr. Jennifer Guida, Ph.D., M.P.H., is a Postdoctoral Fellow in the Basic Biobehavioral and Psychological Sciences Branch in the Behavioral Research Program, Division of Cancer Control and Population Sciences, at the National Cancer Institute (NCI). Dr. Guida is interested in elucidating the biological pathways of psychosocial effects on quality of life for cancer survivors. Dr. Guida received her undergraduate degree in Anthropology from Arizona State University and a Master's in Public Health (M.P.H.) from the University of Colorado. During her M.P.H. training, she was a fellow at the Centers for Disease Control and Prevention in Atlanta, Georgia, in the National Center for HIV/AIDS, viral Hepatitis, STD, and TB Prevention in the Office of the Director. Recently, she completed her doctoral degree in Epidemiology from the University of Maryland, College Park. Her doctoral training integrated techniques in social network analysis, epidemiologic methods, and the social determinants

of health. Dr. Guida became a Summer Research Fellow (2015 and 2016) and special volunteer in the Genetic Epidemiology Branch in the Division of Cancer Epidemiology and Genetics at the NCI exploring the effects of mammographic density on molecular subtypes among Chinese women with breast cancer. Her dissertation work combined her interest in cancer survivorship and social network methods and investigated social network change over time and their effects on mental, physical, and immunologic well-being for cancer survivors.

### Kevin Howcroft, Ph.D.

Dr. Kevin Howcroft is chief of the Cancer Immunology, Hematology, and Etiology Branch of the National Cancer Institute's Division of Cancer Biology.

### Arti Hurria, M.D. *Scientific Steering Committee Chair, Think Tank Co-Chair*

Dr. Arti Hurria is a geriatrician and oncologist and is Vice Provost of Clinical Faculty and Director of the Center for Cancer and Aging at City of Hope. The overall goal of Dr. Hurria's research program is to improve the care of older adults with cancer. Under Dr. Hurria's leadership, the Center for Cancer and Aging has developed and executed over 26 geriatric oncology protocols, enrolling over 3,400 participants on studies focused on cancer and aging. Dr. Hurria is principal investigator on four NIH-funded grants and has received research support from the Breast Cancer Research Foundation, UniHealth Foundation, and Hearst Foundation. Dr. Hurria leads national and international efforts to improve the care of older adults with cancer. She served on the Institute of Medicine, Committee on Improving the Quality of Cancer Care: Addressing the Challenges in an Aging Population. Dr. Hurria serves as the Editor-in-Chief Emeritus for the Journal of Geriatric Oncology (Editor-in-Chief, 2010-2017). She was the recipient of the B.J. Kennedy Award from the American Society of Clinical Oncology, which recognizes scientific excellence in geriatric oncology. Dr. Hurria was elected to the Board of Directors for the American Society of Clinical Oncology in 2016. In 2017, Dr. Hurria was the recipient of an endowed chair in geriatric oncology (The George Tsai Geriatric Oncology Chair) and the recipient of the International Society of Geriatric Oncology Paul Calabresi Award.

### Chamelli Jhappan, Ph.D.

Dr. Chamelli Jhappan is a program director in the Cancer Immunology, Hematology, and Etiology Branch of the National Cancer Institute's Division of Cancer Biology.

### Ronald Kohanski, Ph.D.

Dr. Ronald Kohanski, Ph.D., is the Deputy Director of the Division of Aging Biology at the National Institute on Aging (NIA), National Institutes of Health (NIH). Trained as a biochemist, he obtained a Ph.D. in Biochemistry from the University of Chicago in 1981. After a postdoctoral fellowship with M. Daniel Lane at the Johns Hopkins University School of Medicine, he held a faculty position at the Mount Sinai School of Medicine for 17 years before returning as a faculty member at Johns Hopkins. His fields of research included enzymology and developmental biology of the insulin receptor. Dr. Kohanski joined the Division of Aging Biology, NIA, in 2005 as a Program Officer, and became Division Deputy

Director in 2007. Dr. Kohanski has promoted aging research in the specific areas of stem cell biology and cardiovascular biology. More broadly, he promotes research efforts to expand studies beyond laboratory animals, to address the basic biology of aging explicitly in human populations and non-laboratory animals (domestic and wild populations).

Dr. Kohanski is also a co-founder and co-leader of the trans-NIH Geroscience Interest Group (GSIG). The group spans the entire NIH and is built on the fact that aging is the major risk factor for most chronic age-related diseases. In keeping with this program, Dr. Kohanski has encouraged researchers to consider age as an essential parameter of research using animal models of chronic diseases. More broadly, he promotes research into the basic biology of aging that could explain why aging is itself the major risk factor for chronic diseases.

### Kirsten K. Ness, P.T., Ph.D., F.A.P.T.A.

Dr. Kirsten K. Ness is a physical therapist and clinical epidemiologist and Member of the faculty at St. Jude Children's Research Hospital. She has a B.A. in Physical Therapy, an M.A. in Leadership, and an M.P.H. and Ph.D. in Epidemiology. She is a Catherine Worthingham Fellow of the American Physical Therapy Association and has been in Physical Therapy practice for over 30 years. Her research focuses on the observation and remediation of functional loss among persons who were treated for cancer during childhood. She has funding from the American Cancer Society, the Gabrielle's Angel Foundation, the National Cancer Institute, and the National Institute of Child Health and Human Development. She has over 200 peer reviewed publications and serves on the Steering Committees for the Childhood Cancer Survivor Study and the Children's Oncology Group Survivorship and Outcomes Committee. She is an active member of the Oncology Section of the American Physical Therapy Association, and on the Editorial Boards of Pediatric Physical Therapy, Pediatric Blood and Cancer, Physical Therapy, Rehabilitation Oncology, and the Journal of Clinical Oncology.

### Ann O'Mara, Ph.D., R.N.

Dr. Ann O'Mara is Head of Palliative Research in the National Cancer Institute (NCI) Division of Cancer Prevention. She manages a portfolio of symptom management and palliative and end-of-life care research projects. The majority of these projects focus on the more common morbidities associated with cancer and its treatment, e.g., pain, chemotherapy-induced neuropathy, fatigue, sleep disturbances, and psychosocial issues, such as distress, anxiety and depression. She is a member of several trans-NIH working groups and consortia, e.g., trans-NIH Pain Consortium, established to enhance research and promote collaboration across NIH Institutes and Centers with programs and activities addressing morbidities. Dr. O'Mara has conducted research on end-of-life care, and on educating nurses and physicians about palliative care. Her publications focus on quality-of-life issues facing cancer patients and families across the disease trajectory. Prior to NCI, she was Director of the Advanced Practice Oncology Track, University of Maryland School of Nursing. She is a member of the Oncology Nursing Society, American Society of Clinical Oncology, American Nurses Association, American Pain Society, and International Society for Quality of Life Research; a Fellow in the American Academy of Nursing; and a former editorial board member of the Journal of Clinical Oncology. She has received numerous NIH merit awards for efforts promoting symptom management and quality-of-life research. She received the

Distinguished Alumni Award from the University at Buffalo, the State University of New York, where she received a B.S. in Nursing. She earned an M.S. in Nursing from the Catholic University of America, a Master of Public Health from the Uniformed Services University of the Health Sciences, and a Ph.D. from the University of Maryland, College Park.

### Jennifer Schrack, Ph.D., M.S. *Think Tank Co-Chair*

Dr. Jennifer Schrack, Ph.D., M.S., is an Assistant Professor of Epidemiology with a primary research focus on the role of physiological factors in maintaining mobility and functional independence with aging. She holds a Master's in Exercise Physiology from the University of Michigan and a Ph.D. in Epidemiology from the Johns Hopkins Bloomberg School of Public Health. She has extensive clinical and research experience as an exercise physiologist, with an emphasis on the assessment of laboratory measures of energy expenditure and free-living physical activity using accelerometers. This work has grown to include multiple types of activity and heart rate monitors across numerous studies, including the Baltimore Longitudinal Study of Aging (BLSA), the Study of Physical Resiliency iN Geriatrics (SPRING), the Study to Understand vitamin D and falls in You (STURDY), the Aging, Cognition, and Hearing Evaluation in Elders (ACHIEVE) Randomized Trial, and the Multicenter AIDS Cohort Study (MACS). Her recent research has expanded to include assessment of physiological mechanisms contributing to the development of an accelerated aging phenotype. She recently completed a K01 award from the National Institute on Aging (NIA) focused on investigating differences in functional decline, energy expenditure, and physical activity by HIV-serostatus in the MACS. She is currently the PI of a R21 from the NIA to investigate mechanisms of fatigability in participants of the BLSA, overall and by cancer history, and of a U01 from the NIA to delineate associations among energy regulation, physical activity, and Alzheimer's disease in the BLSA.

### Felipe Sierra, Ph.D.

Dr. Felipe Sierra, Ph.D., is the Director of the Division of Aging Biology at the National Institute on Aging (NIA), National Institutes of Health (NIH). Trained as a biochemist in his native Chile, he obtained a Ph.D. in Biochemistry and Molecular Biology from the University of Florida in 1983. After a postdoc at the University of Geneva, he worked in industry (at Nestlé, still in Switzerland) for the next five years. At this stage he developed his interest in the biology of aging, an interest that brought him back to Academia (and to the United States), as an Assistant Professor at the Medical College of Pennsylvania, and later as an Associate Professor at the Lankenau Institute for Medical Research in Pennsylvania. This last position was shared with a primary appointment at the University of Chile in Santiago. Four years after initiating this arrangement, Dr. Sierra relocated again to the U.S., this time as a Program Director within the Division of Aging Biology, NIA. He became the Director of this unit in April 2006.

Dr. Sierra is also the founder and coordinator of the trans-NIH Geroscience Interest Group (GSIG). The group spans the entire NIH and is built on the fact that aging is the major risk factor for most chronic age-related diseases – Alzheimer's, cardiovascular disease, cancer, and more – and thus understanding the basic biology of aging is central to our ability to address these diseases. In 2013 and 2014 he received NIH Director's Awards for this effort.

### Russell Tracy, Ph.D.

Dr. Russell Tracy is a Professor in the Department of Pathology & Laboratory Medicine in the University of Vermont's Larner College of Medicine. His approach to research reflects his training in biochemistry and clinical chemistry, and his long interest in population-based science. Areas of research include the interrelationships of coagulation, fibrinolysis and inflammation, especially the innate and adaptive immune systems, in the etiology of atherosclerosis and coronary heart disease, insulin resistance and diabetes, HIV-related morbidity and mortality, and other complex diseases, as well as more broadly in the process of aging. The main tools of his laboratory are those of molecular and genetic epidemiology, in the context of multi-center studies and clinical research. More basic biochemical approaches are used in the development of new assays for epidemiological application. Dr. Tracy has a longstanding interest in disease risk modeling and risk assessment as well as in developing new biomarkers for clinical and epidemiological research.

## Invited Speakers

### Daniel W. Belsky, Ph.D.

Dr. Daniel W. Belsky is Assistant Professor in the Department of Population Health Sciences at the Duke University School of Medicine and Social Science Research Institute. Dr. Belsky is a Senior Fellow at the Duke Center for Aging and a Research Scholar at the Duke Population Research Institute. This Winter he will join the faculty in the Department of Epidemiology at Columbia University's Mailman School of Public Health. Dr. Belsky works at the intersection of genetics, the social and behavioral sciences, and public health. His work brings together discoveries from the cutting edge of genome science and longitudinal data from population-based cohorts to identify mechanisms that cause accelerated health decline in older age. Dr. Belsky takes a life-span approach that encompasses research on cohorts of children, young and middle-aged adults, and older adults. His goal is to understand why socioeconomically disadvantaged populations suffer increased morbidity in older age and earlier mortality, and to devise strategies for intervention to mitigate these health inequalities. After finishing his Ph.D. at the UNC Gillings School of Public Health in 2012, Dr. Belsky came to Duke for a postdoc at the Center for The Study of Aging and Human Development. He received his Ph.D. at the University of North Carolina at Chapel Hill in 2012.

### Harvey Jay Cohen, M.D.

Dr. Harvey Jay Cohen, M.D., is Walter Kempner Professor, Director, Center for the Study of Aging and Human Development, Chair Emeritus, Department of Medicine at Duke University Medical Center. Dr. Cohen is the immediate past co-chairs (for 25 years) of the Cancer in the Elderly Committee for The Alliance for Clinical Trials in Oncology. He is immediate past President of the American Federation for Aging Research and a past President of the American Geriatrics Society, the Gerontological Society of America and the International Society of Geriatric Oncology and is PI of the Partnership for Anemia: Clinical and Translational Trials in the Elderly (PACTTE). He received his M.D. from SUNY Downstate Medical College, residency in medicine and fellowship in Hematology-Oncology at Duke University Medical Center. He has published extensively with more than 400 articles and book chapters, with special emphasis on geriatric assessment, biologic basis of functional decline, and cancer and hematologic problems in the elderly. He is co-editor of Geriatric

Medicine, 4th Edition; Practical Geriatric Oncology; and author of the book Taking Care After 50. He has received the BJ Kennedy award from the American Society for Clinical Oncology, and the Paul Calabresi Award from the International Society of Geriatric Oncology, the Kent Award from the Gerontological Society of America, the Joseph T. Freeman Award, and the Jahnigen Memorial Award from the American Geriatrics Society.

### James DeGregori, Ph.D.

Dr. James DeGregori is a Professor in the Department of Biochemistry and Molecular Genetics and the Deputy Director of the University of Colorado Cancer Center. He holds the Courtenay C. and Lucy Patten Davis Endowed Chair in Lung Cancer Research. He received a B.A. in Microbiology from the University of Texas at Austin in 1987, a Ph.D. in Biology from the Massachusetts Institute of Technology in Cambridge in 1993, and postdoctoral training at Duke University Medical Center from 1993-1997.

His lab seeks to understand how carcinogenic conditions promote cancer evolution and to discover pathway dependencies in cancers that can be exploited therapeutically. For the former, his lab studies the evolution of cancer, in the context of their Adaptive Oncogenesis model, with a focus on how aging and other insults influence cancer initiation. His lab has developed this cancer model based on classic evolutionary principles, and substantiated this model by theoretical, experimental and computational studies. Other studies in the lab are geared toward the development of novel therapeutic strategies to treat leukemias and non-small cell lung cancers. These studies have identified signaling, metabolic and mitochondrial vulnerabilities of cancer cells engendered by tyrosine kinase inhibition. These studies led to several Phase I clinical trials.

His lab's overarching goal is to develop a better understanding of cancer, from its causes to its dependencies, that can facilitate the development of better prevention and treatment strategies.

### Luigi Ferrucci, M.D., Ph.D.

Dr. Luigi Ferrucci is a geriatrician and an epidemiologist who conducts research on the causal pathways leading to progressive physical and cognitive decline in older persons. He has made major contributions in the design of many epidemiological studies conducted in the U.S. and in Europe, including the European Longitudinal Study on Aging, the "ICare Dicomano Study," the AKEA study of Centenarians in Sardinia and the Women's Health and Aging Study. He was also the Principal Investigator of the InCHIANTI study, a longitudinal study conducted in the Chianti Geographical area (Tuscany, Italy) looking at risk factors for mobility disability in older persons. Dr. Ferrucci received a Medical Degree and Board Certification in 1980, Board Certification in Geriatrics in 1982 and Ph.D. in Biology and Pathophysiology of Aging in 1998 at the University of Florence, Italy. He spent a two-year internship at the Intensive Care Unit of the Florence Institute of Gerontology and Geriatrics, and was for many years Associate Professor of Biology, Human Physiology and Statistics at the University of Florence. Between 1985 and 2002 he was Chief of Geriatric Rehabilitation at the Department of Geriatric Medicine and Director of the Laboratory of Clinical Epidemiology at the Italian National Institute of Aging. In September 2002, he became the Chief of the Longitudinal Studies Section at the U.S. National Institute on Aging (NIA). From

2002 to 2014 he was the Director of the Baltimore Longitudinal Study on Aging. Dr. Ferrucci is currently the Scientific Director of NIA, since May 2011.

### Leonid A. Gavrilov, Ph.D.

Dr. Leonid A. Gavrilov, Ph.D., is an expert in biodemographic studies of human aging, mortality and longevity. Dr. Gavrilov has over 30 years of professional experience in this area of research and published more than 100 scientific papers on related topics in collaboration with Dr. Natalia S. Gavrilova. They are the authors of the scientific monograph The Biology of Lifespan: A Quantitative Approach, which received positive reviews in a dozen of academic journals including Nature, British Medical Journal and Population Studies. It was selected as recommended reading on the "lifespan" topic by the Encyclopedia Britannica. Dr. Gavrilov is a Principal Investigator of several award-winning research projects, funded by the National Institute on Aging (NIA), Society of Actuaries, European Union and the U.S. Civilian Research and Development Foundation (CRDF). He recently completed a large NIA-funded research project, "Biodemography of Exceptional Longevity in the United States." Dr. Gavrilov is an Editorial Board Member of the scientific peer-reviewed journals Gerontology, Rejuvenation Research, Journal of Demographic Economics, Advances in Aging Research, and Theoretical Biology and Medical Modeling. Dr. Gavrilov is currently working at the Center on Aging, NORC at the University of Chicago. He is a Fellow of the Gerontological Society of America and a member of Population Association of America. He was an invited speaker on aging and longevity topics at international scientific meetings in Australia, Belgium, Canada, Czech Republic, England, France, Germany, Greece, Italy, Japan, Kyrgyzstan, Malaysia, Netherlands, Russia, Spain, Switzerland, and the United States.

### Natalia S. Gavrilova, Ph.D.

Dr. Natalia S. Gavrilova, Ph.D., is an expert in biodemographic methods, population aging, biomarkers of health and sexuality at older ages. She received her Ph.D. in anthropology and population science at the Moscow State University in Russia and then her master's degree in computer science at the University of Chicago. Her research projects were funded by international funding agencies, including the International Science Foundation, the European Union, and the National Institute on Aging (USA). She worked on NIH-funded projects including "Biodemography of Exceptional Longevity in the United States" and "Innovative Network Core on Biomarkers in Population-Based Aging Research (CCBAR)." Currently she is a principal investigator on the NIA-funded project "Biodemography of old-age mortality." Dr. Gavrilova is an invited author in a number of publication projects, including the Macmillan Encyclopedia of Aging, the Encyclopedia of the Life Course and Human Development, International Handbook of Population Aging, Handbook of the Biology of Aging and others. She is an Editorial Board Member of the scientific journal Demografie and a grant reviewer for the National Institute on Aging and the Maurice Falk Institute for Economic Research in Israel. Dr. Gavrilova is a Fellow of the Gerontological Society of America and a member of Population Association of America. She is currently working at the University of Chicago and the Center on Aging, NORC at the University of Chicago.

### Kevin Krull, Ph.D.

Dr. Kevin Krull is a Full Member of the faculty at St. Jude Children's Research Hospital and a Board-Certified Clinical Neuropsychologist with a background in clinical neuropsychology, biological psychology, and cognitive neuroscience. He has developed a research program at St. Jude that focuses on identifying factors associated with individual variability in long-term central nervous system outcomes in survivors of childhood cancer. His research includes lifespan approaches, following children through active therapy and well into adulthood. He employs treatment exposures and biomarkers to predict neurocognitive, brain imaging, and patient-reported outcomes. He has over 150 peer-reviewed publications and is currently the PI on three NIH grants.

### Jeanne Mandelblatt, M.D., M.P.H.

Dr. Jeanne Mandelblatt is a tenured Professor of Medicine and Oncology at Georgetown University. With her cross-disciplinary training in geriatrics, health services research, and cancer epidemiology, Dr. Mandelblatt is a nationally recognized population scientist with more than two decades of continuously, multi-RO1 funded NIH collaborative research focused on cancer, policy, and aging. Dr. Mandelblatt has published more than 235 articles to date with her colleagues, with close to 17,000 citations of this work (H-index of 69). In recognition of her leadership and collaborative scientific accomplishments, Dr. Mandelblatt was awarded a seven-year NCI Outstanding Investigator Grant in 2015 (R35) to study cancer care in older individuals.

In her present aging research, she is studying the effects of breast cancer and its treatments on aging trajectories and domains of function and ability to perform daily tasks. She is also using population-based research findings to drive basic discovery about cancer and aging in animal models, and to use mechanistic insights from the basic science laboratory to inform the next generation of clinically relevant population research studies.

### Deborah K. Mayer, Ph.D., R.N., A.O.C.N., F.A.A.N.

Dr. Deborah K. Mayer, Ph.D., R.N., A.O.C.N., F.A.A.N., currently serves in NCI's Office of Cancer Survivorship. Dr. Mayer is an advanced practice oncology nurse who has over 40 years of cancer nursing practice, education, research, and management experience. She earned a Ph.D. from the University of Utah, her M.S.N. from Yale University, her B.S.N. from Excelsior College, her Nurse Practitioner Certificate from the University of Maryland, and her diploma from Pennsylvania Hospital School of Nursing.

Dr. Mayer is past president of the Oncology Nursing Society (ONS), was a member of the National Cancer Institute's National Cancer Advisory Board (a Presidential appointment) and Board of Scientific Advisors. Dr. Mayer was elected as a fellow of the American Academy of Nursing. She is active in ONS and the American Society of Clinical Oncology (ASCO) and is the Immediate Past Chair of the ASCO Survivorship Committee. Most recently she served as Chair of the ASCO Survivorship Committee. She served as the Editor for the ONS' Clinical Journal of Oncology Nursing (CJON) from 2007-2015 and has published over 150 articles, book chapters and editorials on cancer-related issues. She was awarded the ONS Lifetime Achievement Award in 2015 and, in 2016, was appointed as the only nurse to Vice President Joe Biden's Cancer Moonshot Blue Ribbon Panel. In 2018, she began consulting with the

National Cancer Institute's Division of Cancer Control and Population Sciences on issues related to cancer survivorship.

Dr. Mayer is the Frances Hill Fox Distinguished Professor at the School of Nursing at UNC and the UNC Lineberger Director of Cancer Survivorship. She is the oncology coordinator for the oncology focus of the nurse practitioner program. Her program of research focuses on the issues facing cancer survivors and improving cancer care. She has a clinical practice working with breast cancer survivors. As a nurse who works "frontline" with cancer survivors and as a cancer survivor herself, she brings a unique perspective to her clinical, research and health policy collaborations with cancer survivors, primary care providers, cancer specialists and researchers.

### Nathan Price, Ph.D.

Dr. Nathan Price is Professor & Associate Director of the Institute for Systems Biology in Seattle, where he co-directs with Lee Hood the Hood-Price Integrated Lab for Systems Biomedicine. He is also affiliate faculty at the University of Washington in the Departments of Bioengineering, Computer Science & Engineering, and Molecular & Cellular Biology. He is Co-Founder and on the Board of Directors of Arivale, a scientific wellness company that was named as Geekwire's 2016 startup of the year. He was the recipient of early career awards from the National Institutes of Health, the National Science Foundation, American Cancer Society, the Roy J. Carver Charitable Trust, and Genome Technology. He was also named as a Camille Dreyfus Teacher-Scholar, and received the 2016 Grace A. Goldsmith Award for his work in pioneering "scientific wellness." He serves on numerous advisory boards including for Roche (Personalized Medicine division), Providence St. Joseph Health, Habit, Trelys, Novo Nordisk Foundation Center for Biosustainability, Science Translational Medicine and Cell Systems.

### Stephanie Studenski, M.D., M.P.H.

Dr. Stephanie Studenski is a geriatrician and rheumatologist whose practice, teaching and research focus on physical function, mobility, balance disorders and falls in later life. Originally trained as a nurse as well as physician, she also has a Master's Degree in Public Health. Through her research, she strives to understand age-related problems in physical function. Her recent work focuses on the role of the central nervous system and body composition in mobility and physical function. She is recently retired from her position as Chief of the Longitudinal Studies Section of the Intramural Research Program of the National Institute on Aging and Director of the Baltimore Longitudinal Study of Aging. She is currently Professor Emeritus at the University of Pittsburgh.

### Erwin J. Tan, M.D.

Dr. Erwin J. Tan, M.D., is the Director of Thought Leadership, Health, at AARP and a board-certified internist and geriatrician. Dr. Tan previously served as the director of Senior Corps at the Corporation for National and Community Service. From 2004 to 2010, he served as an Assistant Professor of Medicine at the Johns Hopkins School of Medicine, where he was an attending physician in the Division of Geriatric Medicine. He was also a co-investigator in the Baltimore Experience Corps Study. From 2003-2004, Dr. Tan was a White House Fellow

serving as a Special Assistant to the Secretary of Veterans Affairs. Before coming to the Washington, D.C., Metropolitan area, he was a faculty member at the University of California, San Francisco School of Medicine, where he served as Geriatric Medicine Fellow and a Primary Care Medicine Resident. He was commissioned as a 2nd Lieutenant in the United States Army Reserves. Dr. Tan received a bachelor's from Brown University and graduated from New York University School of Medicine as a member of the Alpha Omega Alpha honor society. He was born in Indonesia and is a naturalized citizen of the United States.

### Olga Theou, Ph.D.

Dr. Olga Theou is an Assistant Professor of Medicine at Dalhousie University. She is also an Affiliated Scientist of Geriatric Medicine with the Nova Scotia Health Authority and an Adjunct Senior Lecturer of Medicine with the University of Adelaide in Australia. She obtained her Bachelor of Science in Physical Education and Sports Sciences at Aristotle University in Greece, Master's of Science in Gerokinesiology from the California State University in Fullerton, and Ph.D. in Health and Rehabilitation Sciences with specialization in Health and Aging from Western University. In 2013, she was awarded a Banting Fellowship, which recognizes exceptional individuals deemed likely to contribute positively to Canada's economic, social and research based growth. Her research interests include aging, frailty and physical activity, and she has been ranked fourth in Canada and 11th worldwide in frailty expertise by Expertscape.

Appendix C: DCCPS Research Fact Sheet

**NIH) NATIONAL CANCER INSTITUTE**   Division of Cancer Control and Population Sciences

The Division of Cancer Control and Population Sciences (DCCPS) is interested in better understanding the short- and long-term effects of cancer and its treatment on well-being and trajectories of aging during survivorship. Research funded by DCCPS in this area also aims to strengthen measurement validity, including symptomatic toxicities of treatment and consequent multimorbidity factors. This research also supports patient-generated data to stratify risk, support decision-making, and optimize cancer and aging outcomes in older adults.

### AREAS OF RESEARCH EMPHASIS IN CANCER AND AGING

- Identification of aging phenotypes in cancer survivors, mechanisms underlying the emergent phenomena, and mitigation of unintended aging-related outcomes in cancer survivors due to cancer and its treatment
- Use of population-based data and existing data resources to address cancer and aging hypotheses
- Implications of aging-related changes in body composition, diet, stress, sleep patterns, medication, oral environment, environmental exposures, and lifestyle behaviors for cancer risk and outcomes
- Measurement of biological, behavioral (e.g., energy balance), and psycho-social (e.g., depression, isolation) risk factors for multimorbidity
- Interventions to address the complexity of symptom management in older adults
- Inclusion of older adults in intervention and observational studies

### SELECTED FUNDING OPPORTUNITY ANNOUNCEMENTS RELEVANT TO CANCER AND AGING

Leveraging Cognitive Neuroscience Research to Improve Assessment of Cancer Treatment-Related Cognitive Impairment
PAR-18-605/R01 and PAR-18-606/R21
Contact: Jerry Suls, Ph.D. | Jerry.Suls@nih.gov | 240-276-6811

Intervening with Cancer Caregivers to Improve Patient Health Outcomes and Optimize Health Care Utilization
PAR-18-246/R01
Contact: Michelle Mollica, Ph.D., M.P.H., R.N., O.C.N. | Michelle.Mollica@nih.gov | 240-276-7621

Reducing Overscreening for Breast, Cervical, and Colorectal Cancers among Older Adults
PA-18-015/R21 and PA-18-005/R01
Research Infrastructure Development for Interdisciplinary Aging Studies
PAR-18-645/R21/R33
Contact: Erica Breslau, Ph.D., M.P.H. | Breslaue@mail.nih.gov | 240-276-6773

Oral Anticancer Agents: Utilization, Adherence, and Health Care Delivery
PA-17-060/R01 and PA-17-061/R21
Contact: Wendy Nelson, Ph.D., M.P.H. | nelsonw@mail.nih.gov | 240-276-6971

## CANCER AND ACCELERATED AGING: ADVANCING RESEARCH FOR HEALTHIER SURVIVORS

This initiative represents a collaboration of the National Cancer Institute, the National Institute on Aging, and representatives from cancer research institutions throughout the country. The series of three think-tank meetings aims to identify research gaps and promising approaches to improve our ability to understand, predict, and mitigate aging-related consequences of cancer and cancer treatment.

The series will begin July 25-26 in Rockville, Maryland, with "Measuring Aging and Identifying Aging Phenotypes in Cancer Survivors." During this meeting, participants will strive to elucidate the best methods to measure aging among cancer survivors, identify aging phenotypes, and produce a strategic and unified vision to fill the identified research gaps and establish methodological approaches to characterize aging phenotypes.

Future think tanks will work toward identifying the cancer-survivor populations where gaps in knowledge on aging trajectories exist, resources available to examine aging trajectories, analytical methods and modeling approaches to best address relevant research questions, and strategies to prevent, slow, or reverse accelerated aging trajectories among cancer survivors.

## DCCPS CANCER AND ACCELERATED AGING SCIENTIFIC CONTACTS

Paige Green, Ph.D., M.P.H., F.A.B.M.R.
Chief
Basic Biobehavioral and Psychological Sciences Branch
Behavioral Research Program
Paige.Green@nih.gov | 240-276-6899

Lisa Gallicchio, Ph.D.
Program Director
Clinical and Translational Epidemiology Branch
Epidemiology and Genomics Research Program
Lisa.Gallicchio@nih.gov | 240-276-5741

U.S. Department of Health & Human Services | National Institutes of Health

Appendix D: Critical Questions

**NIH NATIONAL CANCER INSTITUTE**

**Division of Cancer Control and Population Sciences**

**Cancer & Accelerated Aging** ADVANCING RESEARCH FOR HEALTHIER SURVIVORS

**Measuring Aging And Identifying Aging Phenotypes In Cancer Survivors**

## Questions to Guide/Prompt Think Tank Deliberations

### IDENTIFYING "AGING PHENOTYPES" AND UNDERSTANDING THE TRAJECTORY(IES) OF AGING AMONG CANCER SURVIVORS

1. What is the definition of a healthy life span or healthy aging after cancer treatment? How is health span regarded in a cancer survivorship context?

2. Does the increased prevalence in age-related comorbidities, higher inflammatory profiles, etc., in cancer survivors, compared with age-matched cancer-free individuals, represent premature ("accelerated") aging, or does it reflect specific outcomes related to cancer diagnosis and treatment toxicity, and/or side effects?

   a. Is it possible to elucidate unique "hallmarks of aging" within the context of cancer survivorship?

   b. Are we essentially interested in secondary aging? Do cancer and cancer treatment result in "injuries" to the organism that cause aging or a change in the rate of aging? Can secondary malignancies be thought of as a secondary aging outcome?[1]

3. What are the aging phenotypes in the general population?

4. How do we best measure aging?

### MECHANISMS BY WHICH CANCER/CANCER TREATMENT LEAD TO ACCELERATED AGING (OR AGING PHENOTYPES)

5. What mechanisms lead to accelerated aging?

6. Recognizing that animal models (typically young-aged animals) are extensively utilized to phenocopy human cancers and test therapeutic approaches, do animal models accurately reflect the accelerated aging observed in humans? Can these models be improved to better understand and investigate accelerated aging pathways and develop novel interventions to stabilize or reverse aging processes?

7. How do aging processes influence cancer biology and progression?

8. How do aging and cancer processes interact in the inflammation/coagulation pathways?

9. How do cancer treatments impact aging? How can cancer and cancer treatment be used to further our understanding of the molecular pillars of aging?

    a. Are the primary targets of these drugs leading to accelerated aging?

    b. Are the side effects of these drugs leading to accelerated aging?

    c. Many of these drugs lead to apoptosis in the targeted cell. Is it possible that there are too many apoptotic bodies for the system to remove, and these produce aging effects?

    d. How do therapy-induced senescent cells contribute to age-related consequences of cancer treatment exposure?

    e. Which senescence-related chemotherapy side effects are due to SASP-induced immune activation? Which immune components?

    f. Which senescence-related chemotherapy side effects are due to SASP factors independent of the immune system? Which factors?

    g. Does getting cancer treatment during a specific life stage (e.g., puberty, pregnancy, or menopause) lead to increased toxicity or disrupt natural aging/development?

10. How much of the distal damage caused by tumors is due to tumor-induced immune activation? Which components?

### EARLY DIAGNOSIS AND SURVEILLANCE OF ACCELERATED AGING

11. What treatment toxicity profiles can be used as early warning signs for loss of function over time?

12. Can a panel of clinical/biological tests be used to identify and monitor progression to "aging phenotypes" in cancer survivors?

13. Can the Tipping Point Theory be used to describe aging among cancer survivors?[2-4] If so, what is the tipping point, and what are the pre-symptomatic early warning signs?

14. Can we measure the loss of resilience earlier in adulthood before the occurrence of frailty?

### RISK AND PROTECTIVE FACTORS

15. What risk factors result in a temporary setback or a continual decline? What changes are protective? Are the changes reversible?

16. What are the risk factors that lead to prefrail/frail states in older adults and that are predictive in younger individuals?

17. How do we protect physiological/functional reserve, protect against chronic multiple organ dysfunction, and build resilience to promote a healthy life span after cancer treatment?

18. Are there "exceptional responders," or individuals/groups whose measures of aging are not accelerated after cancer therapy? Can these individuals/groups be identified and studied?

19. Do accelerated aging trajectories differ by cancer treatment, cancer population/age group, etc.?

20. Is there a differential impact on the rate of aging that depends more on the type and stage of the cancer and less on the therapy? If so, are the effects additive, multiplicative, synergistic?

21. Do high global pro-senescence stress and a compromised immune system lead to accelerated aging?

22. Do certain cancer treatments increase survivors' vulnerability to multiple diseases? How does this intersect with aging, which also increases vulnerability to multiple diseases?

23. What are the best biomarkers, cellular and molecular characteristics that predict or protect from age-related consequences of cancer treatment exposure?

### DESIGNING STUDIES OF CANCER AND ACCELERATED AGING

24. How can we study the mechanisms that lead to accelerated aging?

25. How do we obtain experimental evidence?

26. Are there existing studies (or "banks" of information) that could serve as the infrastructure to measuring aging-related phenotypes longitudinally to investigate aging-related trajectories among cancer survivors?

27. Can risk-prediction models be developed? If so, what do we need to develop models of adverse health outcomes that change the rate of aging? How granular do we need to focus to extrapolate from individual to population-level effects? What is the utility of these risk-prediction models? Should this information be incorporated into clinical decision-making (risk/benefits of certain treatments)?[5,6]

28. Can multi-level systems modeling approaches be used to understand what accelerated aging is and what the phenotype looks like beyond the measurement of one biomarker? Can they be used to: 1) identify individuals who need interventions, and 2) develop personalized cancer rehabilitation interventions?

29. Which advanced statistical analysis techniques hold potential for understanding how brain structure and function change with aging and in response to insults to the brain caused by cancer and cancer treatments?

30. Which models are most appropriate to use to study how brain structure and function change with age and by cancer treatment?

31. Which models describe the resiliency and failure of complex systems? Which are the most appropriate for guiding research related to the interactions of aging processes, cancer, and cancer treatments in determining cognitive aging?

References

1.      Ng, A. K., Kenney, L. B., Gilbert, E. S. & Travis, L. B. Secondary malignancies across the age spectrum. in *Seminars in radiation oncology* **20**, 67–78 (Elsevier, 2010).
2.      Scheffer, M. *et al.* Early-warning signals for critical transitions. *Nature* **461**, 53 (2009).
3.      Olde Rikkert, M. G. M. *et al.* Slowing Down of Recovery as Generic Risk Marker for Acute Severity Transitions in Chronic Diseases. *Crit. Care Med.* **44**, 601 (2016).
4.      Trefois, C., Antony, P. M., Goncalves, J., Skupin, A. & Balling, R. Critical transitions in chronic disease: transferring concepts from ecology to systems medicine. *Curr. Opin. Biotechnol.* **34**, 48–55 (2015).
5.      Salz, T. *et al.* Are we ready to predict late effects? A systematic review of clinically useful prediction models. *Eur. J. Cancer* **51**, 758–766 (2015).
6.      Frobisher, C. *et al.* Risk stratification of childhood cancer survivors necessary for evidence-based clinical long-term follow-up. *Br. J. Cancer* **117**, 1723 (2017).