

# Accelerated Aging Following Cancer Treatment

THE 27TH ANNUAL MARYLAND STATE COUNCIL ON CANCER CONTROL CONFERENCE

Jennifer Guida, PhD, MPH

Program Director

Basic Biobehavioral and Psychological Sciences Branch

Behavioral Research Program

Division of Cancer Control and Population Sciences

# Objectives

1

Describe the links between aging, cancer, and cancer treatment

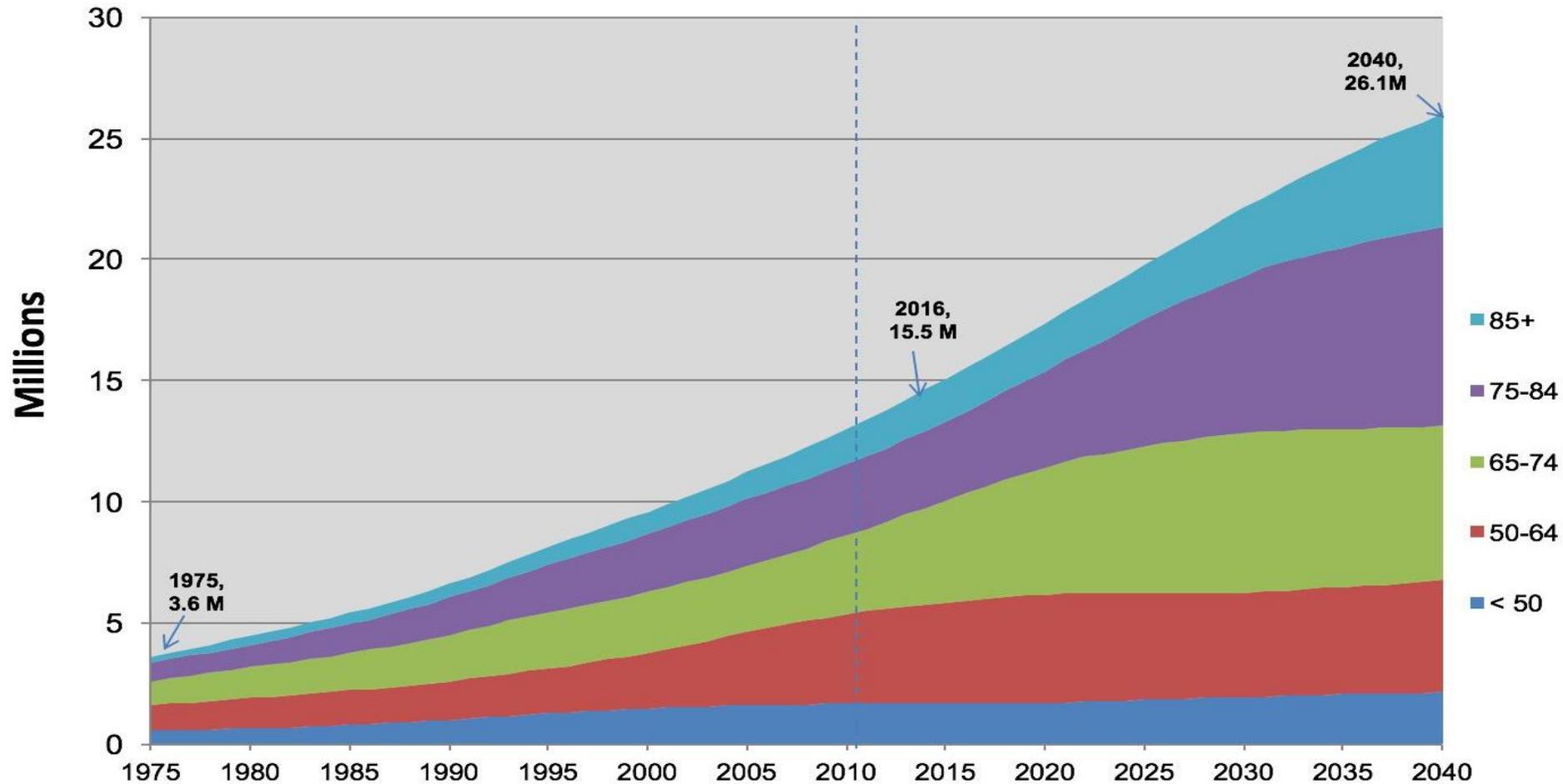
2

Identify opportunities for intervention in cancer survivors

3

Share programmatic opportunities to further research in this area

# Estimated Cancer Prevalence by Age in the U.S. Population from 1975-2040



----- Signifies the year at which the first baby boomers (those born 1946-1964) turned 65 years old

# Living With the Effects of Cancer

*“The aftermath of having cancer is still with me. The damage to my tear ducts has resulted in several painful operations on my eyes to insert prosthetic tear ducts into the nasolacrimal duct to drain the fluid in my eyes. The tubes only provide brief relief and have to be cleaned every 6 to 8 months, necessitating additional surgery. I also have lingering neuropathy in my hands and feet, as well as ongoing achiness from anastrozole. **As a result, I feel decades older than my 61 years.**”*

- Pati Schembari, breast cancer survivor



Source: ASCO, Patient's Corner  
Published March 10, 2017

# Living With the Effects of Cancer

*“I wonder if closer monitoring for chemotherapy side effects could have prevented some of the long-term problems I still contend with, but I try to stay positive. I know how lucky I am to be alive, and I’m grateful that I’ve had 10 more years to be with my family and experience the joys of everyday life. Now, I’m looking forward to the next 10.”*

- Pati Schembari, breast cancer survivor



Source: ASCO, Patient’s Corner  
Published March 10, 2017

# Living With the Effects of Cancer

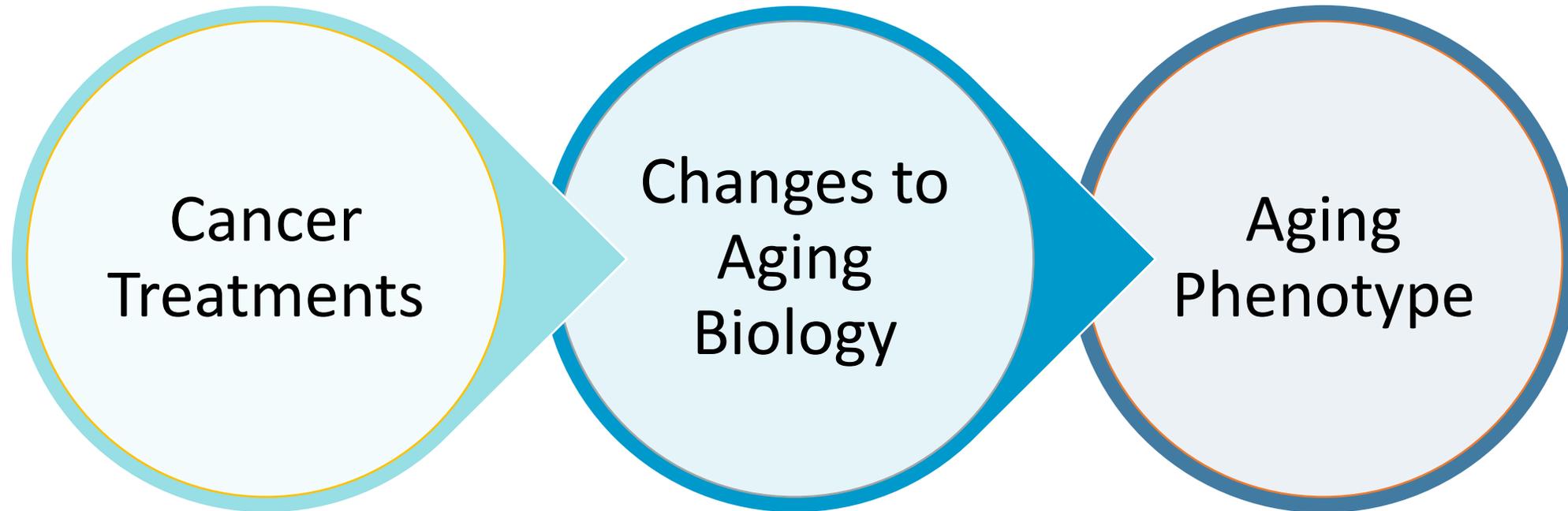
*“Over the years, the cumulative effects of chemotherapy on my body have necessitated a hip replacement due to avascular necrosis of my hip joint, and damage done to my heart requires regular monitoring for hypertension. I try to offset these late effects from treatment by maintaining a regular exercise routine and eating a healthy diet, but I recognize that my life expectancy has probably been shortened, so I make the most of every day.”*

*-Patrick Eck, ALL survivor diagnosed at 17 years*



Source: ASCO Post, Patient's Corner  
Published January 25, 2019

# Cancer Treatments Create Damage that may Accelerate Aging Processes



Cancer Treatments

- Surgery
- Radiation
- Chemotherapy
- Immunotherapy

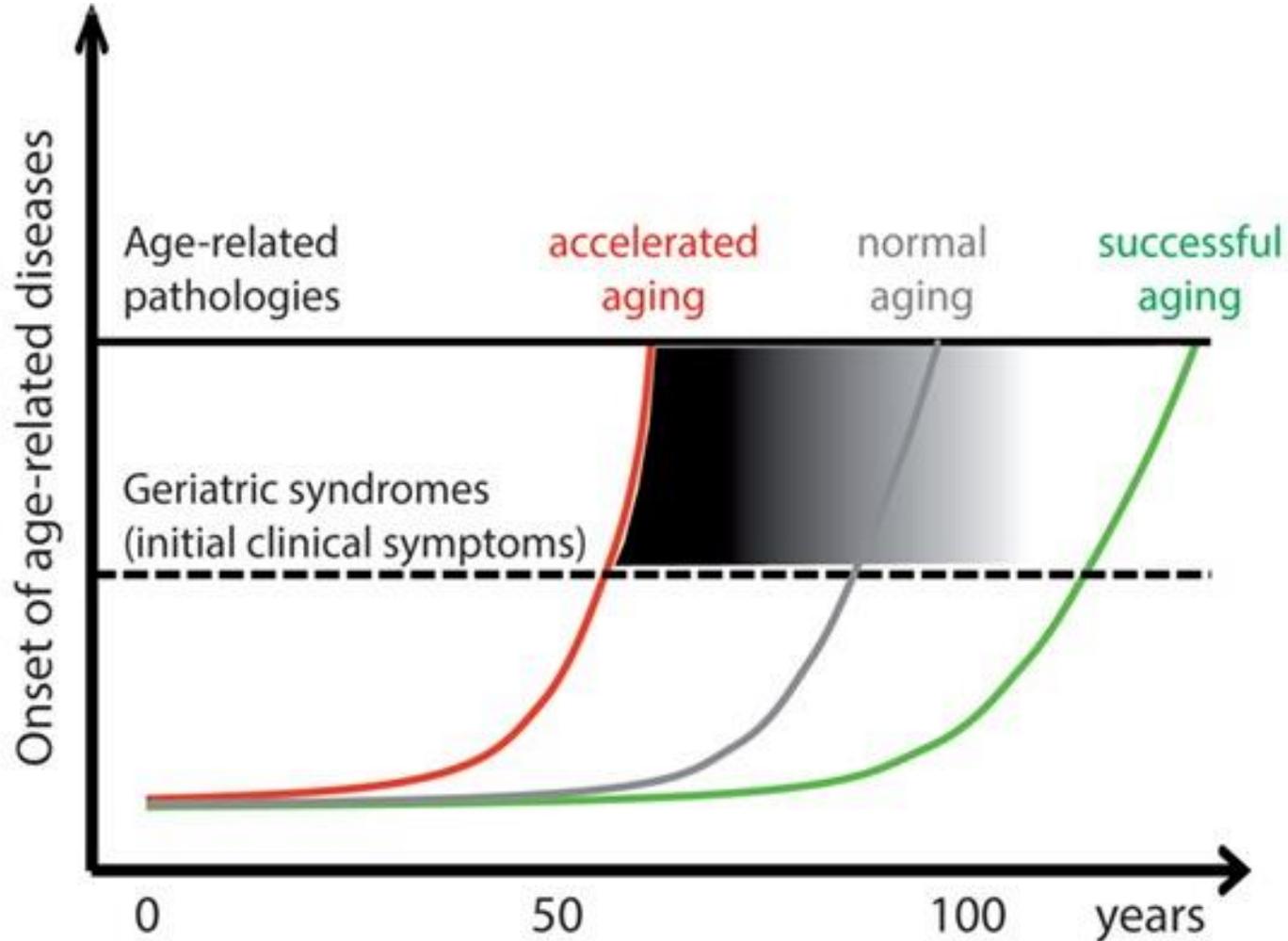
Changes to Aging Biology

- Genomic Instability
- Telomere Attrition
- Epigenetic Alteration
- Loss of Proteostasis
- Deregulated Nutrient Sensing
- Mitochondrial Dysfunction
- Cellular Senescence
- Stem Cell Exhaustion
- Altered Intracellular Comm.

Aging Phenotype

- Frailty
- Sarcopenia
- Chronic Conditions
- Cognitive Impairment
- Functional Decline

# Accelerated Aging is the Onset of Age-Related Conditions Earlier than Normally Expected



# Lingering Impact of Cancer Therapy

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## Cancer Survivors Report:

- Poorer Physical Function
- Poorer Quality of Life
- Increased # of Comorbidities
- Cognitive Decline

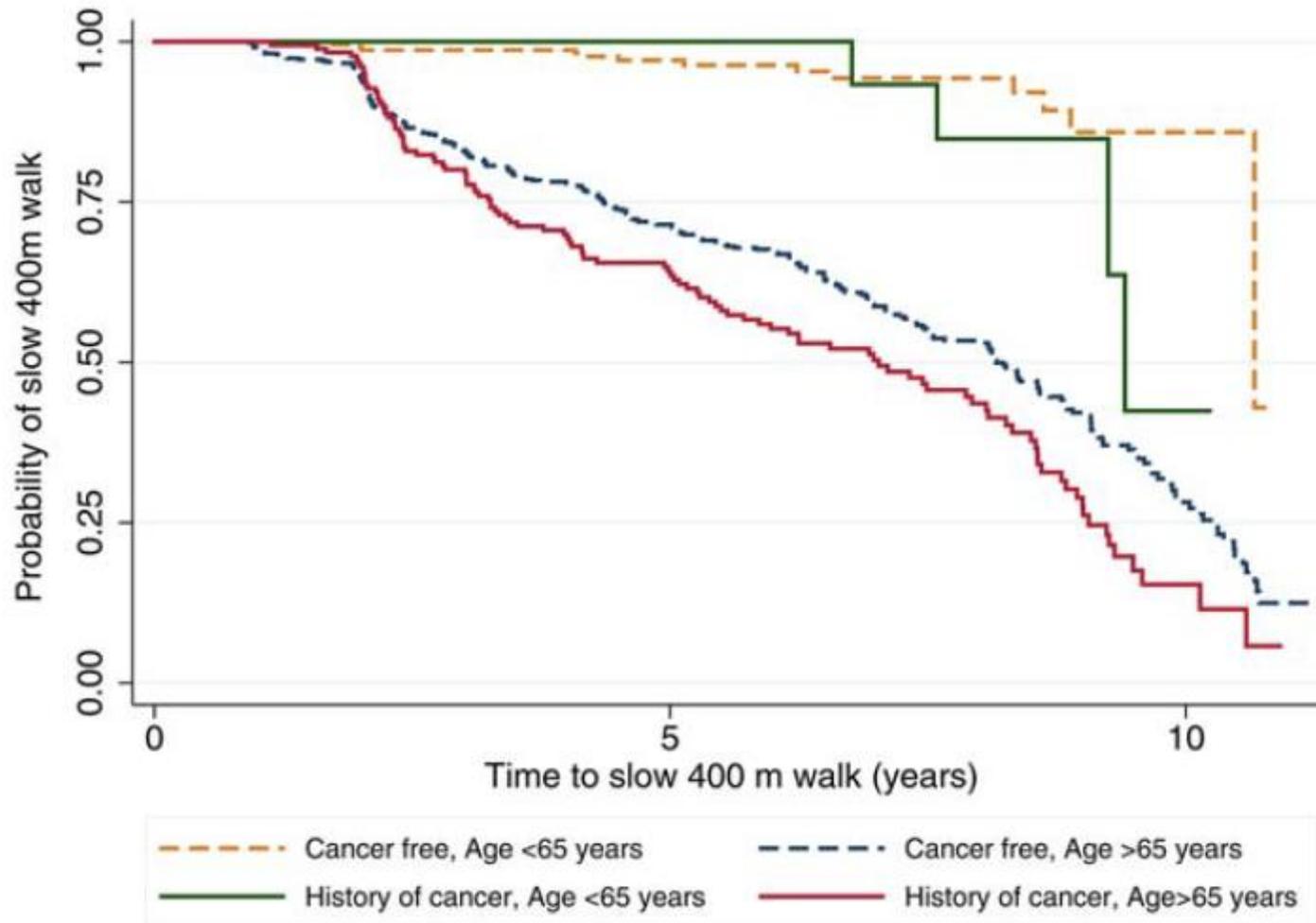
*Hewitt et al. J Ger A Biol Sci Med Sci 2003*  
*Diemling et al. Cancer Nurs. 2007*  
*Gresham et al. Cancer 2018*

*Reeve et al. J Natl Cancer Inst. 2009*  
*Weaver et al. CEBP 2012*

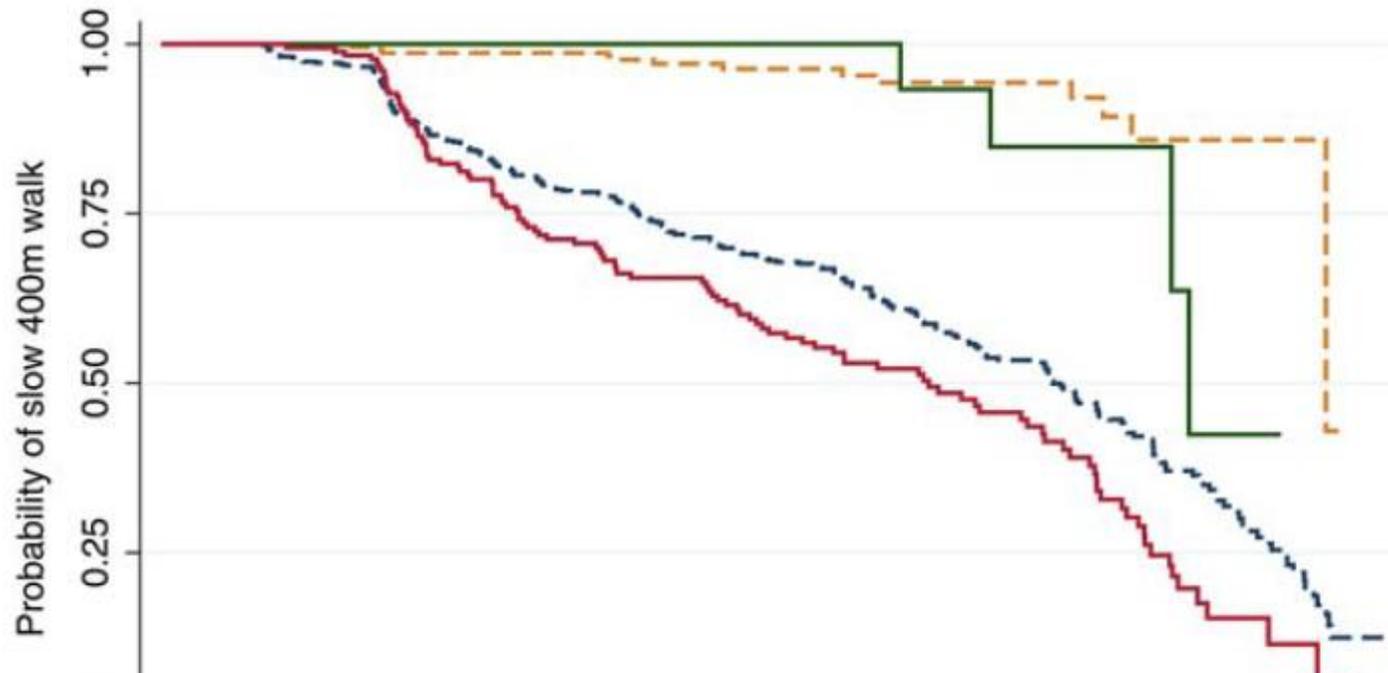
*Baker et al. Cancer 2003*  
*Mariotto et al. CEBP 2007*  
*Gibson et al., Lancet Oncol, 2018*

*Mandelblatt et al. J Clin Oncol. 2014, 2018*  
*Wildiers et al. J Clin Oncol. 2014*

# Cancer Survivors Experience Limitations in Physical Performance



## Cancer Survivors Experience Limitations in Physical Performance



- < 65 years + cancer = 42% greater risk of low endurance
- $\geq$  65 years + cancer = 8.3x greater risk of low endurance

# Evidence of Accelerated Aging in Adult Survivors of Childhood Cancer

- Slower walk speed<sup>1</sup>
- Weaker hand grip strength<sup>1</sup>
- Higher burden of chronic conditions<sup>2</sup>
  - Heart attack
  - Stroke
  - Congestive Heart Failure
- Second cancers<sup>3</sup>
- Frailty<sup>4</sup>



Photo credit: SETH DIXON/ST. JUDE CHILDREN'S RESEARCH HOSPITAL

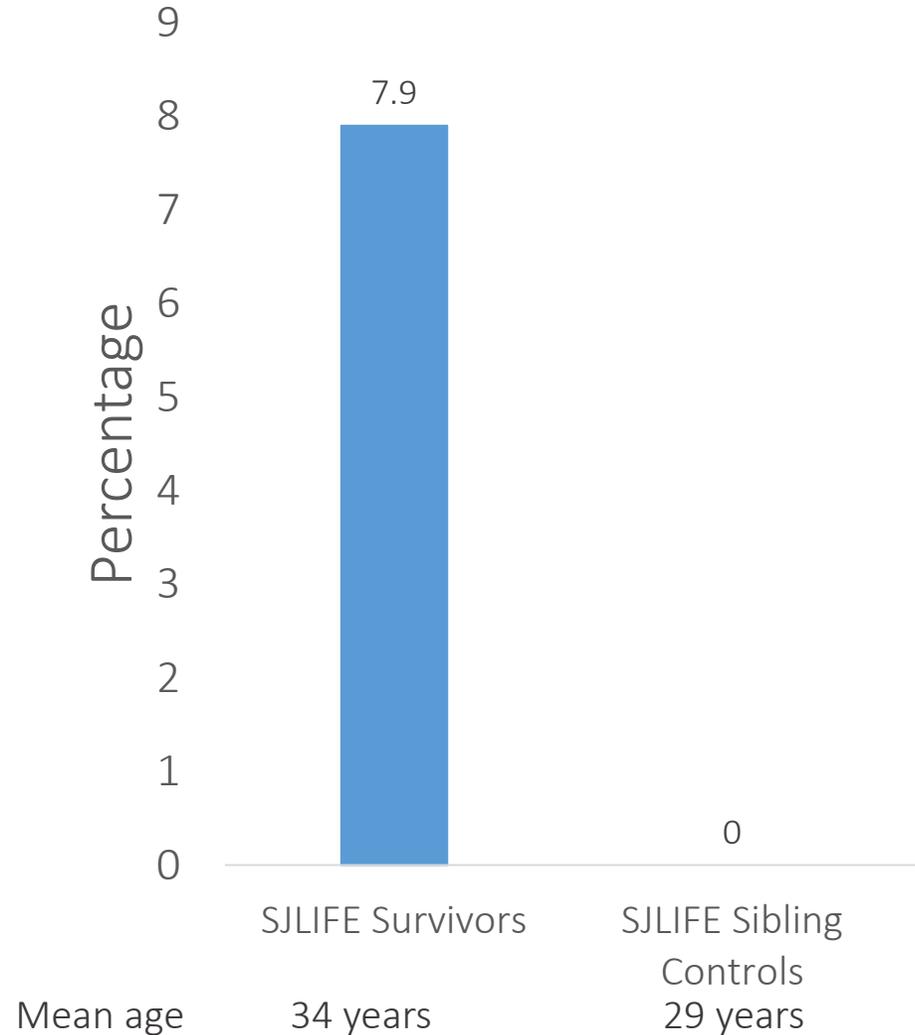
<sup>1</sup>Ness et al., *Cancer*, 2010, 2012

<sup>2</sup>Armstrong et al., *J of Clinical Oncology*, 2014

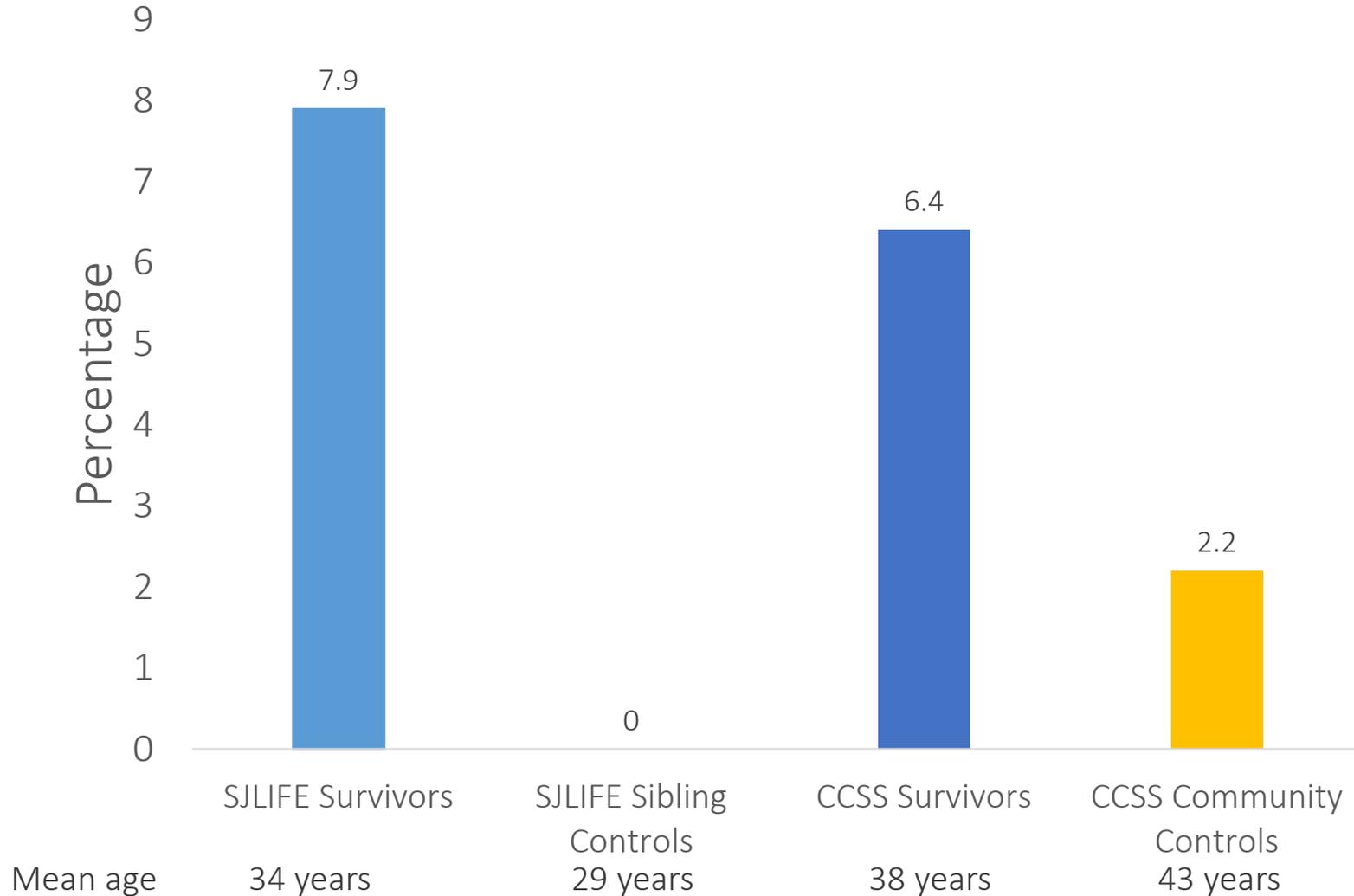
<sup>3</sup>Neglia et al., *JNCI*, 2001

<sup>4</sup>Ness et al., *J Clinical Oncology*, 2018

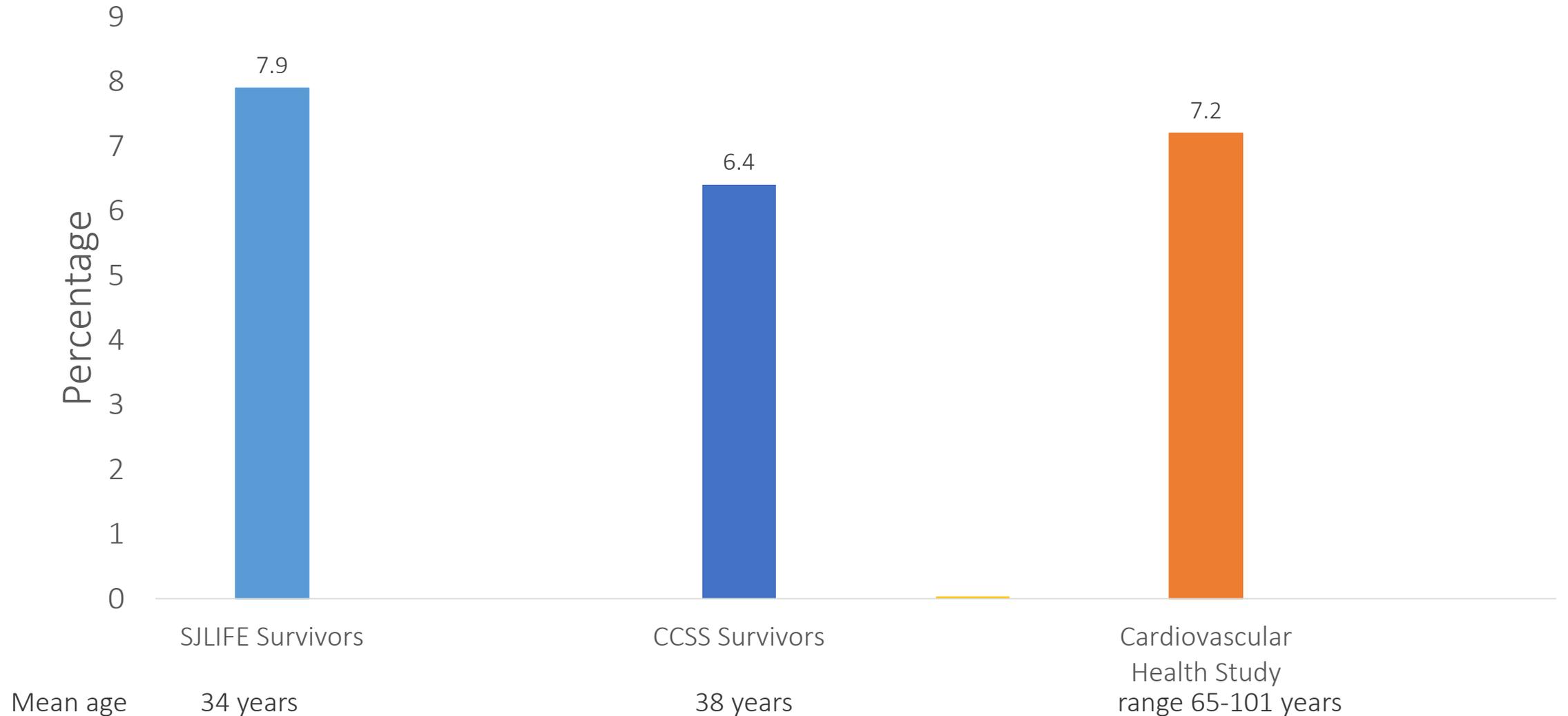
# Prevalence of Frailty in Adults Survivors of Childhood Cancer



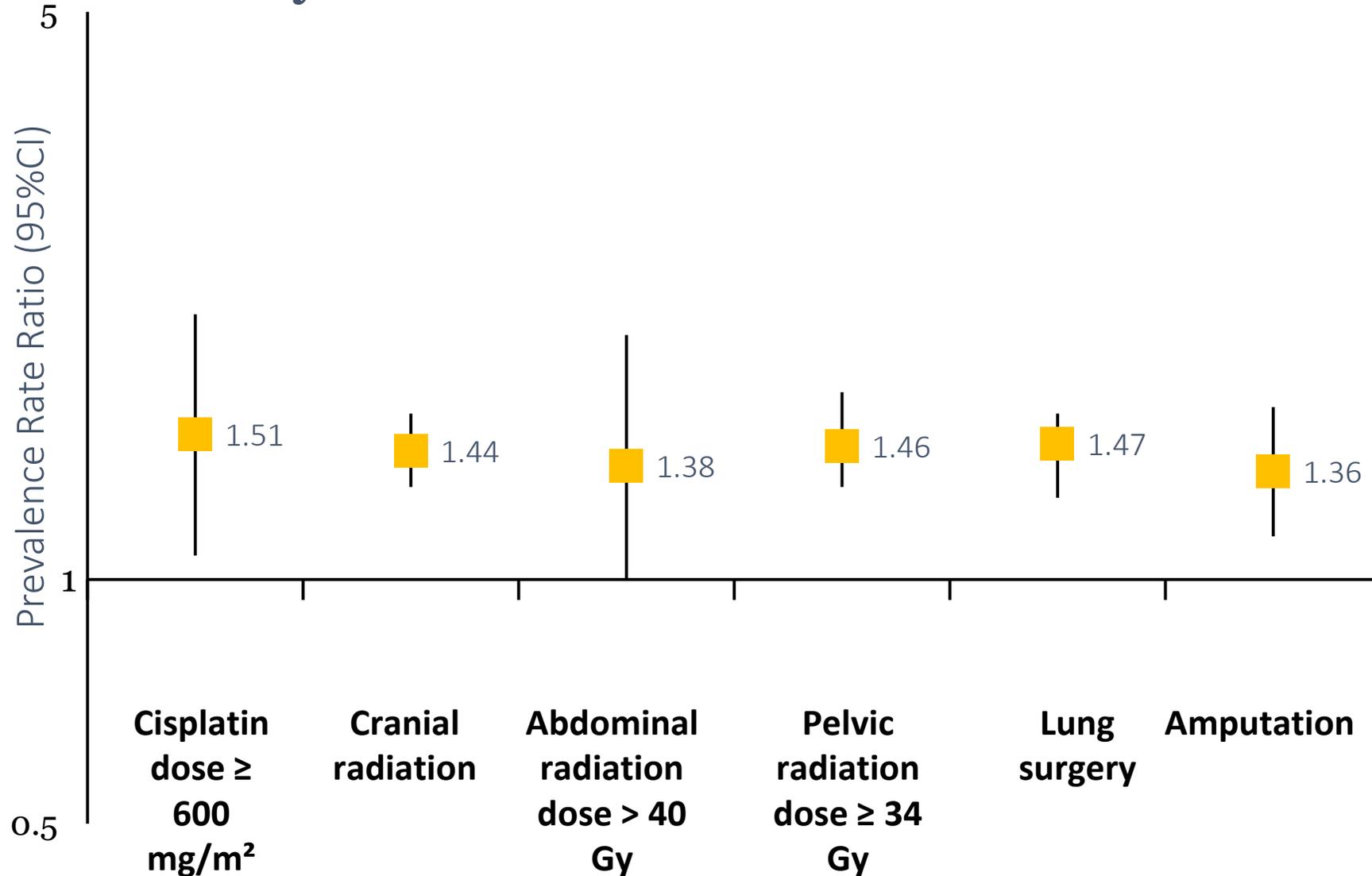
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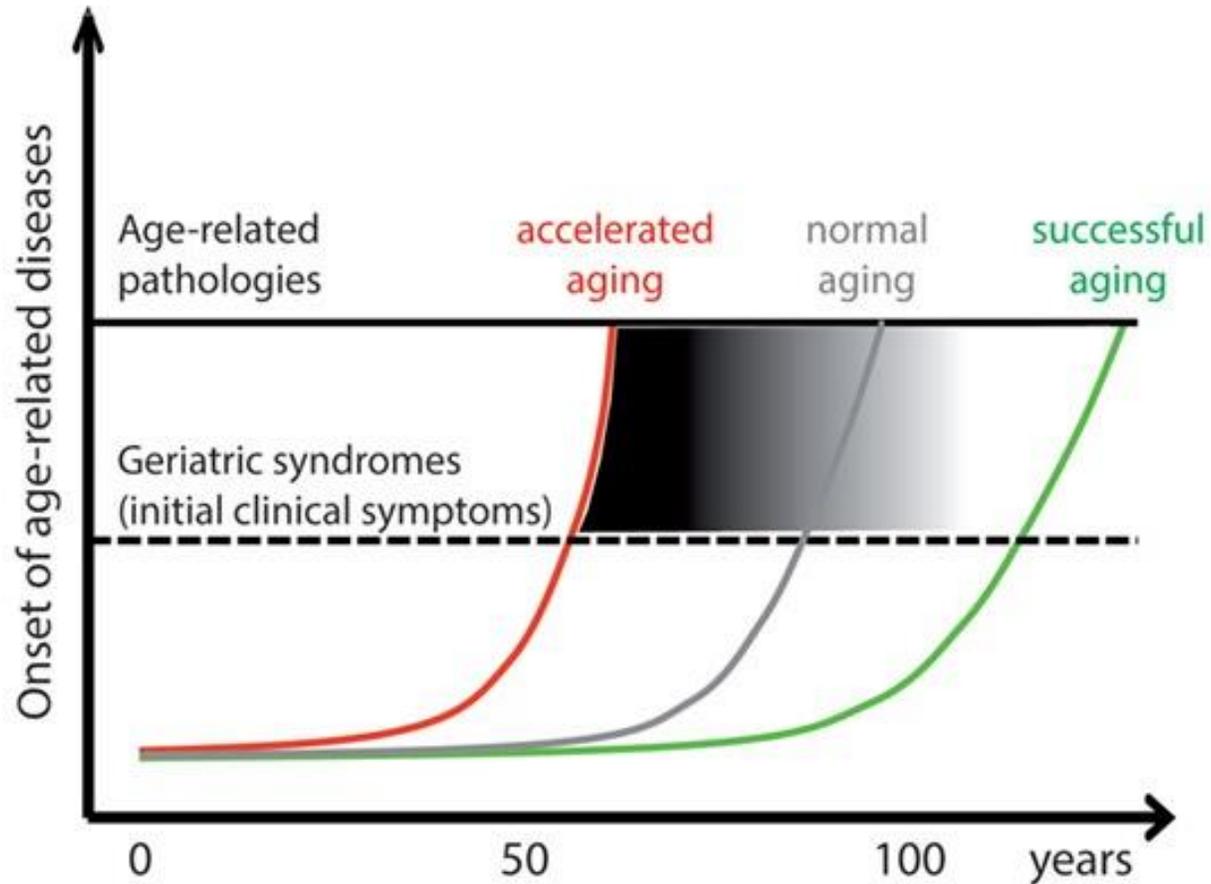
# Cancer Treatment Exposure is Associated with Frailty in Adult Survivors of Childhood Cancer



# Implications for Clinical Care

- Higher healthcare costs + provider shortages
- Clinical interventions are needed to optimize survivorship care:
  - Screening tools and long-term surveillance are needed to identify treatment-related effects
  - Infrastructure to improve communication between patients, oncology and primary care providers
  - Patient education is needed to facilitate informed decision-making
  - Efficacious interventions to prevent or mitigate the aging consequences of cancer treatment

# Summary



## Key Points

- Cancer therapies can damage normal tissues leading to acute, chronic, & late-emerging effects
- Survivors experience a higher burden of age-related conditions compared to controls
- Strong evidence of premature aging in adult survivors of childhood cancer



# Interventions to Prevent or Reverse Cancer- and Treatment-Related Aging

# Childhood Cancer Survivors: Combat Premature Aging



**Some survivors show signs of early aging (frailty).<sup>1</sup> Young adult survivors are more likely than their peers to be frail.**

## Signs may include:

- Weakness
- Exhaustion
- Low lean muscle mass
- Slow walking speed
- Low activity levels



## Take control and fight frailty!



**Talk** to your doctor regularly



Pursue **resistance training** and physical activities that you enjoy



Reach and maintain a **healthy weight**

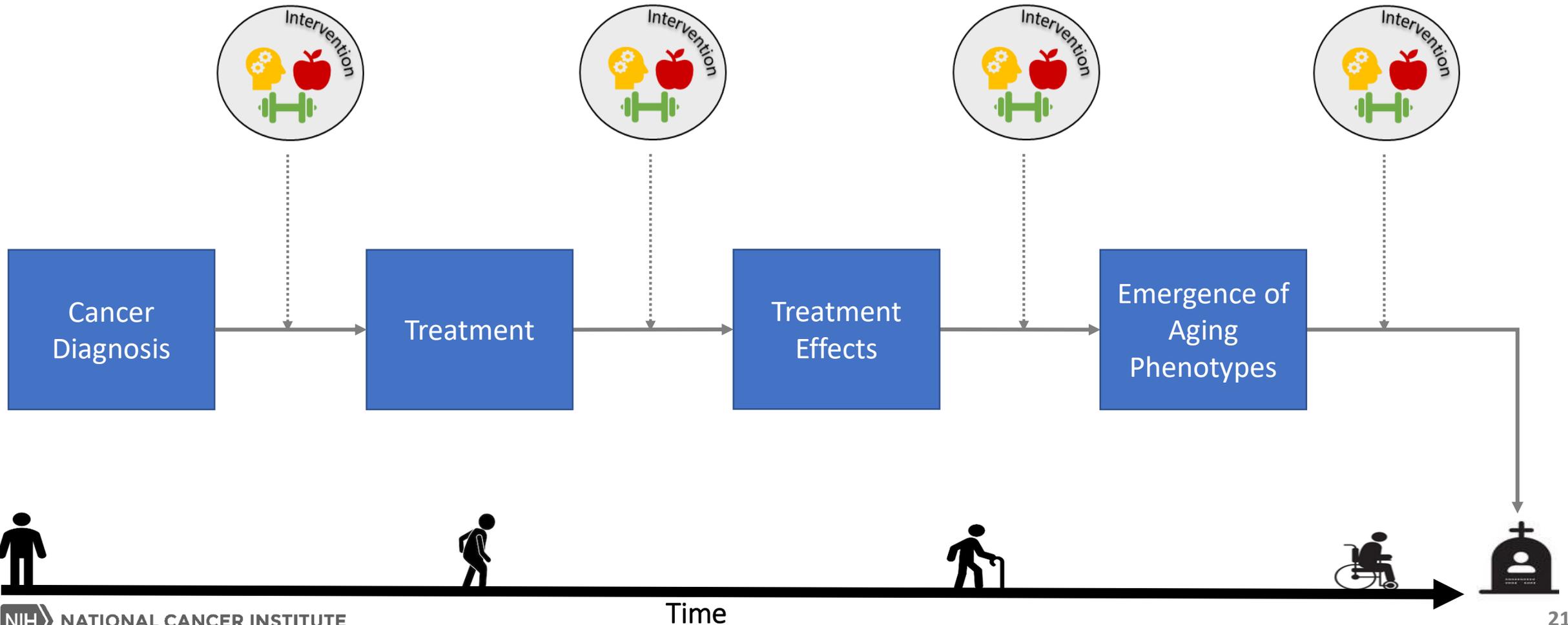


**Avoid smoking**

<sup>1</sup>Ness, K.K. et al., *J Clin Oncol*. 2013

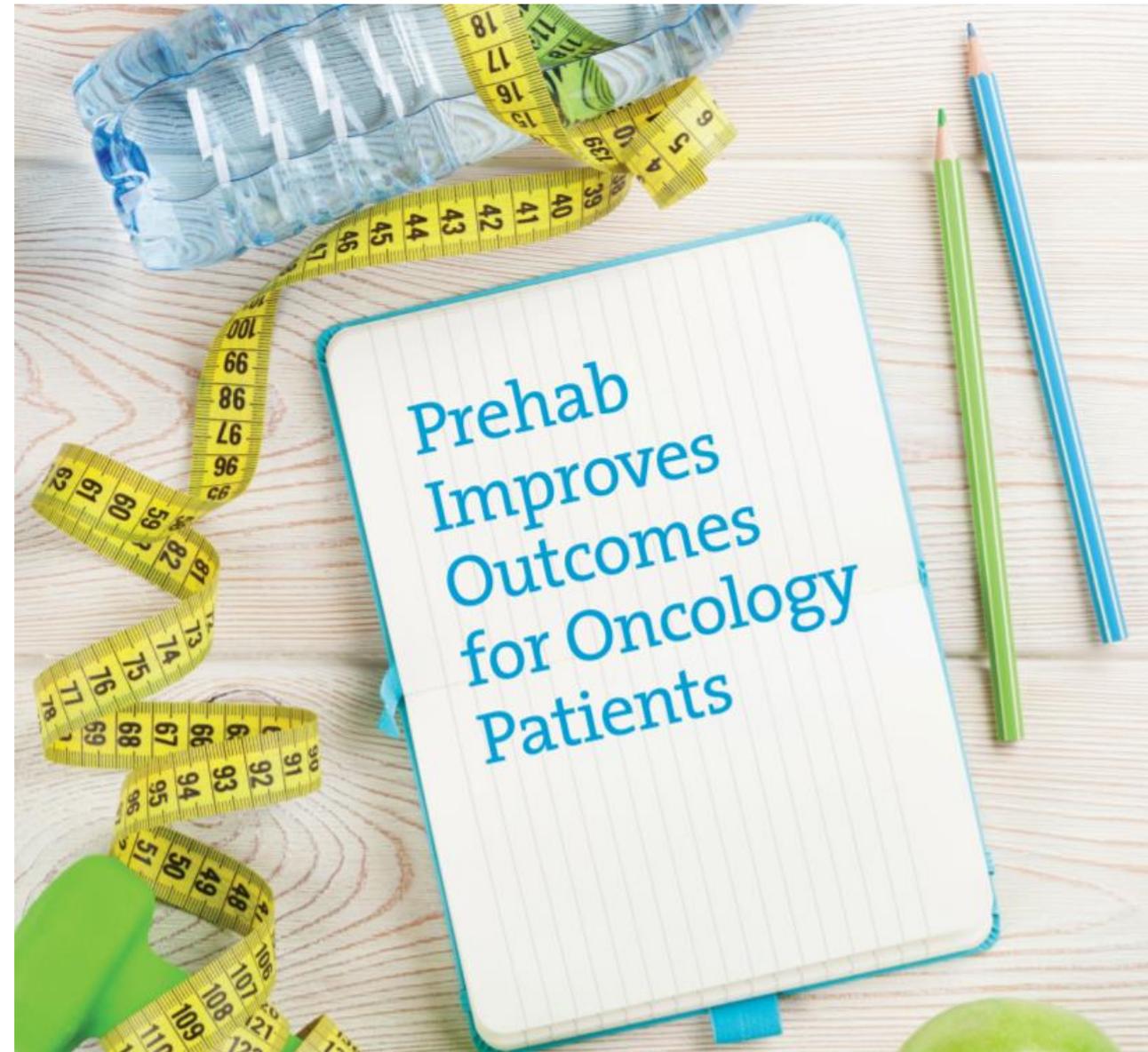
[www.stjude.org/early-aging](http://www.stjude.org/early-aging)

# When is the Best Time to Intervene?



# Prehabilitation Interventions

- Exercise interventions *before* cancer treatment
- Goal is to strengthen patients before the rigors of treatment
- Studies suggest:
  - Improved post-treatment functional status & quality of life<sup>1,2</sup>
  - Reduced risk of postoperative complications<sup>1</sup>
  - Decreased hospital length of stay, healthcare costs, & readmissions<sup>3</sup>



<sup>1</sup>Mayo et al., *Surgery*, 2011

<sup>2</sup>Garcia et al., *Interactive CardioVascular and Thoracic Surgery*, 2016

<sup>3</sup>Philipson et al., *Am J Manag Care*, 2013

# Multicomponent Interventions

## The Reach-out to ENhance Wellness (RENEW) trial

- Two-arm, single-blinded, cross-over study
  - Exercise + Diet (low fat, plant-based diet)
- 641 older, overweight/obese, long-term survivors of breast, prostate, and colorectal cancer
- Intervention improved:
  - Diet quality
  - Physical activity
  - Weight loss
  - Physical function



Morey et al., *JAMA*, 2013

Demark-Wahnefried et al., *J Clin Oncol.*, 2012 23

# Targeting Biological Aging Processes May Prevent or Delay Age-Related Conditions

Intervention	Aging Process
<b>Behavioral Interventions</b>	
Physical activity	Reduce chronic inflammation, mitigate age-related telomere attrition, alteration of DNA methylation patterns
Caloric restriction/intermittent fasting	Decreased IGF signaling, mTOR inhibition
<b>Pharmacologic Interventions</b>	
Metformin	Activation of telomerase expression, reduction of reactive oxygen species, decreased IGF signaling
Senolytics (e.g. bcl-2 inhibitors)	Induction of apoptosis via disabling of anti-apoptotic pathways in senescent cells. Improves metabolic dysfunction, osteoporosis, frailty, muscle wasting
mTOR inhibitors (e.g. rapamycin)	Delays aging phenotype, promotes protein autophagy, extends lifespan

# Key Points

- Surveillance + intervention throughout survivorship may minimize treatment effects
- Combining multiple intervention approaches and targeting aging biology may prevent age-related conditions in cancer survivors

## Childhood Cancer Survivors: Combat Premature Aging



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- Low lean muscle mass
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**Take control and fight frailty!**

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-  Pursue **resistance training** and physical activities that you enjoy
-  Reach and maintain a **healthy weight**
-  **Avoid smoking**

St. Jude Children's Research Hospital  
ALLIANCE FOR EARLY AGING PREVENTION

<sup>1</sup>Ness, K.K. et al., *J Clin Oncol*. 2013

[www.stjude.org/early-aging](http://www.stjude.org/early-aging)



# The Path Forward

NCI's Investment in Cancer- and Treatment-Related Aging

# Cancer & Accelerated Aging

ADVANCING RESEARCH FOR HEALTHIER SURVIVORS



## Objective:

To identify research gaps & promising approaches to improve our understanding of, and ability to predict and mitigate, the short- and long-term aging-related consequences of cancer and treatment



JOURNAL of the  
NATIONAL CANCER INSTITUTE

## Measuring Aging and Identifying Aging Phenotypes in Cancer Survivors <sup>FREE</sup>

Jennifer L Guida, Tim A Ahles, Daniel Belsky, Judith Campisi, Harvey Jay Cohen, James DeGregori, Rebecca Fuldner, Luigi Ferrucci, Lisa Gallicchio, Leonid Gavrilov ... [Show more](#)

[Author Notes](#)

*JNCI: Journal of the National Cancer Institute*, Volume 111, Issue 12, December 2019, Pages 1245–1254, <https://doi.org/10.1093/jnci/djz136>

**Published:** 18 July 2019 **Article history** ▼



JOURNAL of the  
NATIONAL CANCER INSTITUTE

ACCEPTED MANUSCRIPT

## Strategies to Prevent or Remediate Cancer and Treatment-Related Aging <sup>FREE</sup>

Jennifer L Guida, PhD, MPH, Tanya Agurs-Collins, PhD, Tim A Ahles, PhD, Judith Campisi, PhD, William Dale, MD, PhD, Wendy Demark-Wahnefried, PhD, RD, Jorg Dietrich, MD, PhD, Rebecca Fuldner, PhD, Lisa Gallicchio, PhD, Paige A Green, PhD, MPH, FAMBR ... [Show more](#)

*JNCI: Journal of the National Cancer Institute*, djaa060, <https://doi.org/10.1093/jnci/djaa060>

**Published:** 29 April 2020 **Article history** ▼

# Measures of Aging to Consider in Studies of Cancer and Aging

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## Clinical Measures of Aging

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- Gait Speed
- Timed Up and Go
- Grip Strength
- Fried (CHS) Frailty Phenotype
- Deficit Accumulation Index/ Frailty Index
- Cognitive Assessments
  - Hopkins Verbal Learning Test-Revised
  - Controlled Oral Word Association Test
  - The Trail Making Test
  - FACT-Cog
  - PROMIS (Cognitive Function)

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## Biological Measures of Aging

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- 31p Recovery Time
- P16INK4a
- DNA Methylation Epigenetic Clocks:
  - Hannum's clock
  - Horvath's clock
  - PhenoAge

# Opportunities to Expand the Evidence Base

**Identify Aging  
Phenotypes &  
Mechanisms**



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**Methodological &  
Measurement  
Approaches**



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**Methodological &  
Measurement  
Approaches**



**Interventions**



# Opportunities to Expand the Evidence Base

**Identify Aging Phenotypes & Mechanisms**



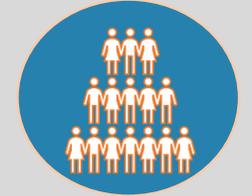
**Methodological & Measurement Approaches**



**Interventions**



**Population-Based Studies**



# Opportunities to Expand the Evidence Base

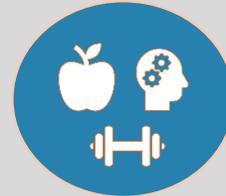
**Identify Aging Phenotypes & Mechanisms**



**Methodological & Measurement Approaches**



**Interventions**



**Population-Based Studies**



**Tools to Stratify Risk & Support Decision-Making**



# Opportunities to Expand the Evidence Base

**Identify Aging Phenotypes & Mechanisms**



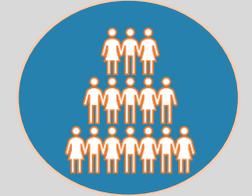
**Methodological & Measurement Approaches**



**Interventions**



**Population-Based Studies**



**Tools to Stratify Risk & Support Decision-Making**



**Implications of Aging on Cancer Risk/Outcomes**



# Opportunities to Expand the Evidence Base

**Identify Aging Phenotypes & Mechanisms**



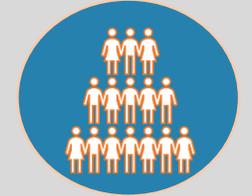
**Methodological & Measurement Approaches**



**Interventions**



**Population-Based Studies**



**Tools to Stratify Risk & Support Decision-Making**



**Implications of Aging on Cancer Risk/Outcomes**



**Surveillance of Risk Factors**



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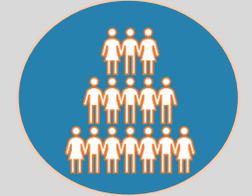
**Methodological & Measurement Approaches**



**Interventions**



**Population-Based Studies**



**Tools to Stratify Risk & Support Decision-Making**



**Implications of Aging on Cancer Risk/Outcomes**



**Surveillance of Risk Factors**



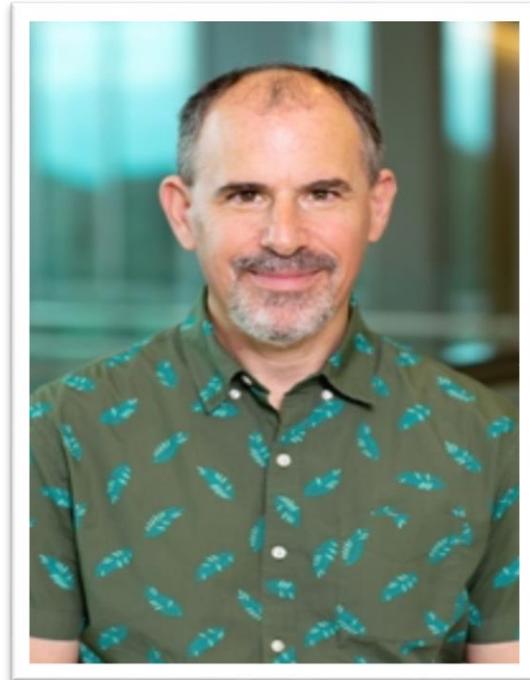
**Inclusion of Older Adults**





# Select Cancer and Aging Funding Opportunities

# Select Funding Opportunities



- Leveraging Cognitive Neuroscience Research to Improve Assessment of Cancer Treatment-Related Cognitive Impairment
- [PAR-19-340/R01](#) and [PAR-19-339/R21](#)
- Todd S Horowitz, PhD  
[Todd.Horowitz@mail.nih.gov](mailto:Todd.Horowitz@mail.nih.gov) | 240-276-6963

# Select Funding Opportunities



- Improving Outcomes in Cancer Treatment-Related Cardiotoxicity
- [PAR-19-112/R01](#)
- Nonniekaye Shelburne, MS, CRNP  
[Nshelburne@mail.nih.gov](mailto:Nshelburne@mail.nih.gov) 240-276-6897

# Select Funding Opportunities



- Clinical Characterization of Cancer Therapy-induced Adverse Sequelae and Mechanism-based Interventional Strategies
- [PAR-19-325](#)
- Kelly Filipski PhD, MPH  
[filipskikk@mail.nih.gov](mailto:filipskikk@mail.nih.gov) | 240-276-6841

# Perspectives on Cancer & Aging

ARTI HURRIA MEMORIAL WEBINAR SERIES



**Arti Hurria, M.D.**  
**(1970-2018)**

## Past Speakers:

- Supriya Mohile, MD, University of Rochester
- William Dale, MD, City of Hope
- Kiri Ness, PhD, St. Jude Children's Research Hospital
- Monica Gramatges, MD, Baylor College of Medicine
- Luigi Ferrucci, MD, National Institutes on Aging
- Morgan Levine, PHD, Yale University
- Hyman Muss, MD, University of North Carolina
- Grant Williams, MD, University of Alabama at Birmingham
- Michael Irwin, MD, University of California, Los Angeles
- Kerri Winters-Stone, PhD, Oregon Health & Science University
- Garnet Anderson, PhD, Fred Hutchinson Cancer Center
- Elizabeth Cespedes Feliciano, PhD, Kaiser Permanente



“If you want to go fast, go alone,  
but if you want to go far, go together.”  
- Arti Hurria, M.D. (1970-2018)

## Acknowledgements



Paige Green, PhD



Lisa Gallicchio, PhD

## Contact Information

Jennifer Guida, PhD, MPH

Basic Biobehavioral and Psychological Sciences Branch

Behavioral Research Program

Division of Cancer Control and Population Sciences

[Jennifer.Guida@nih.gov](mailto:Jennifer.Guida@nih.gov)

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