Perspectives on Cancer & Aging

ARTI HURRIA MEMORIAL WEBINAR SERIES

JANUARY 14, 2020

Canaries in the Coal Mine: What We Can Learn about Aging from Survivors of Childhood Cancer?

A WEBINAR TRIBUTE TO DR. ARTI HURRIA

Kiri K. Ness, P.T., Ph.D., F.A.P.T.A.
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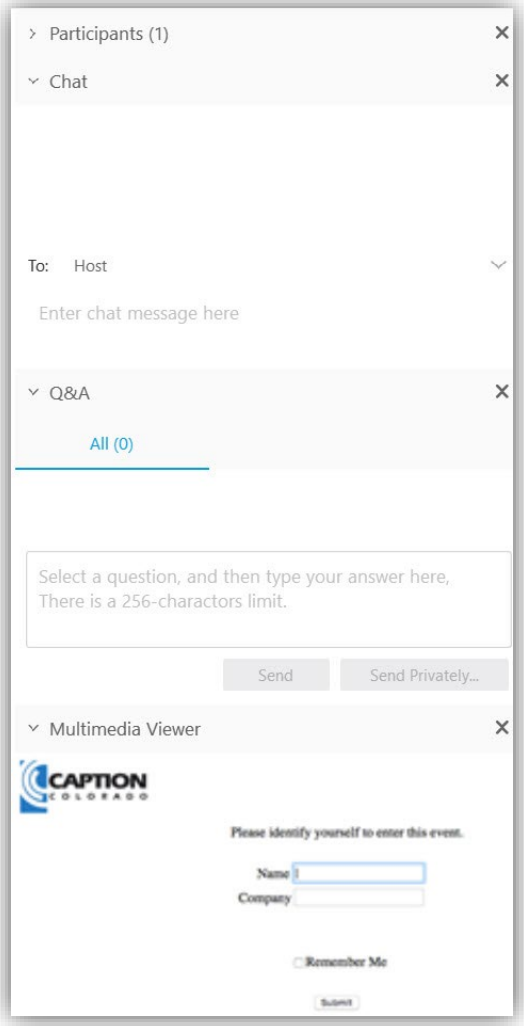
Cancer & Aging Research Group

NIH NATIONAL CANCER INSTITUTE

Using WebEx and webinar logistics



- All lines will be in listen-only mode
- Make sure icons are selected for them to appear as a drop-down option
- Submit questions at any time during the presentation by typing into the Q&A feature on the right-hand side of the WebEx interface.
  - Select Host and a moderator will ask the questions on your behalf
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- This webinar is being recorded

Canaries in the coal mine: What can we learn about aging in survivors of childhood cancer?

Perspectives on Cancer and Aging: Arti Hurria Memorial Webinar Series

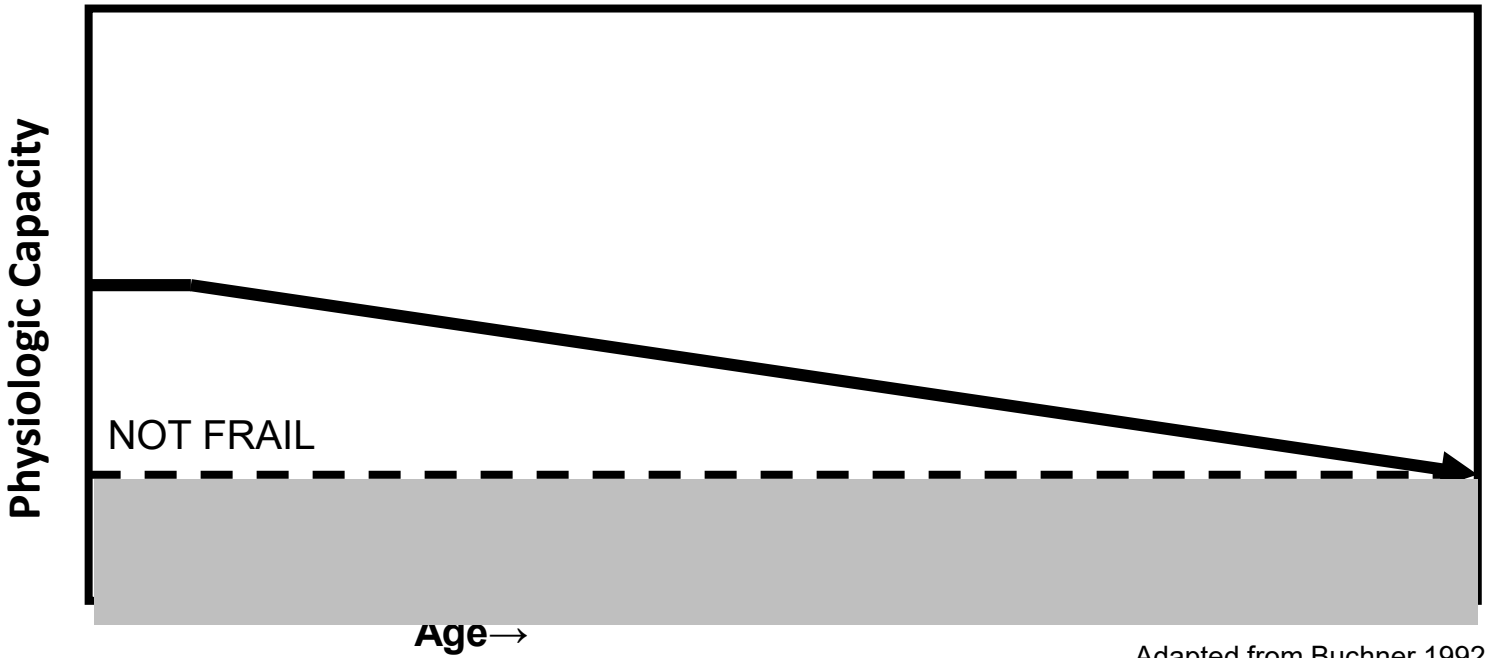
January 14, 2020

Objectives

- Describe frail health in childhood cancer survivors
- Identify specific physiologic targets for intervention in childhood cancer survivors
- Begin to understand the pathobiology of frail health in childhood cancer survivors
- Identify opportunities for prevention of frail health in childhood cancer survivors

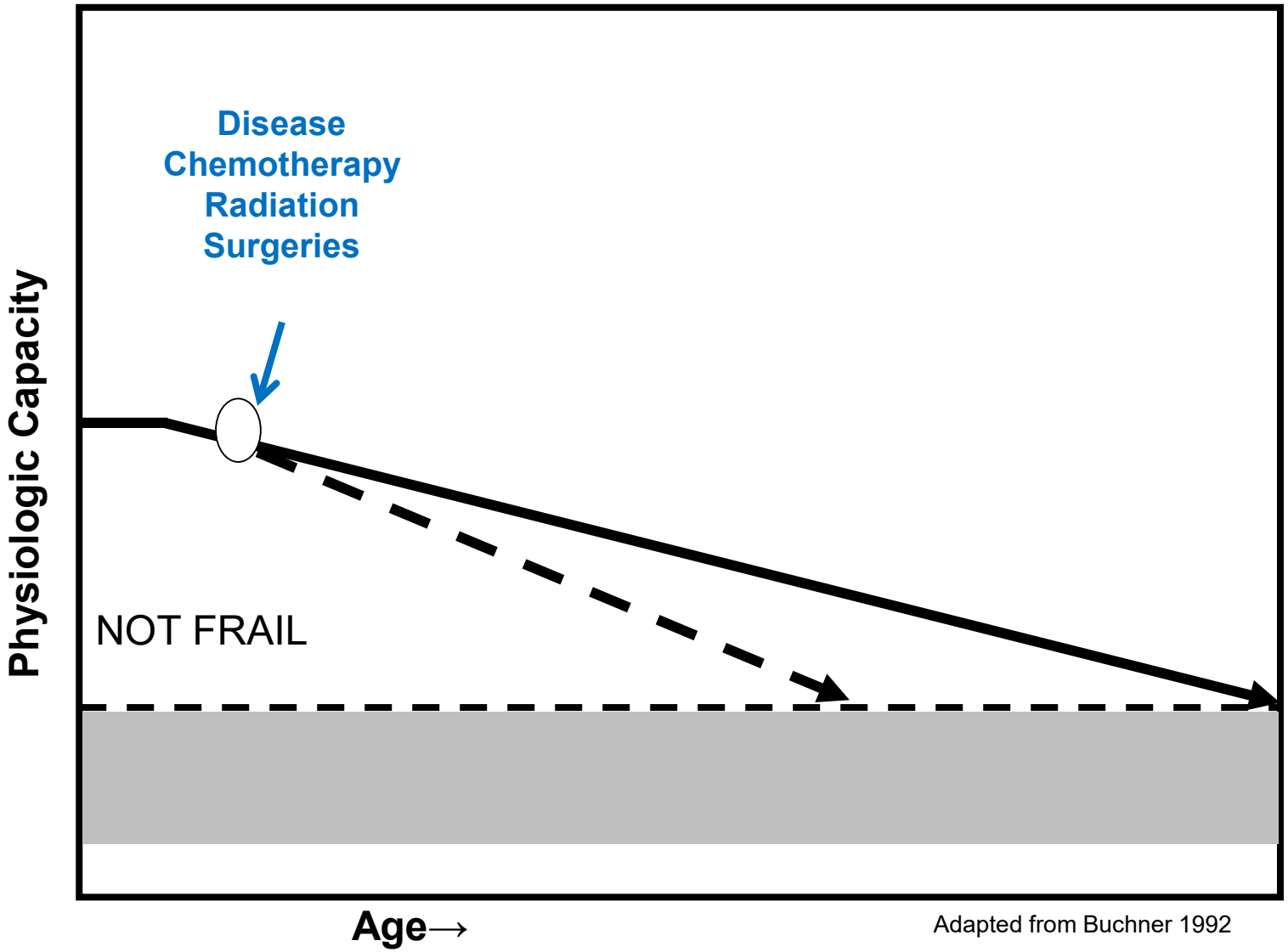
Frailty

- Loss of physiological capacity that interferes with normal function
- Most commonly described in older adults
  - can be distinguished from disability and co-morbidity
  - identifies individuals highly vulnerable to adverse health outcomes, often precedes chronic disease onset, and is a predictor of early mortality



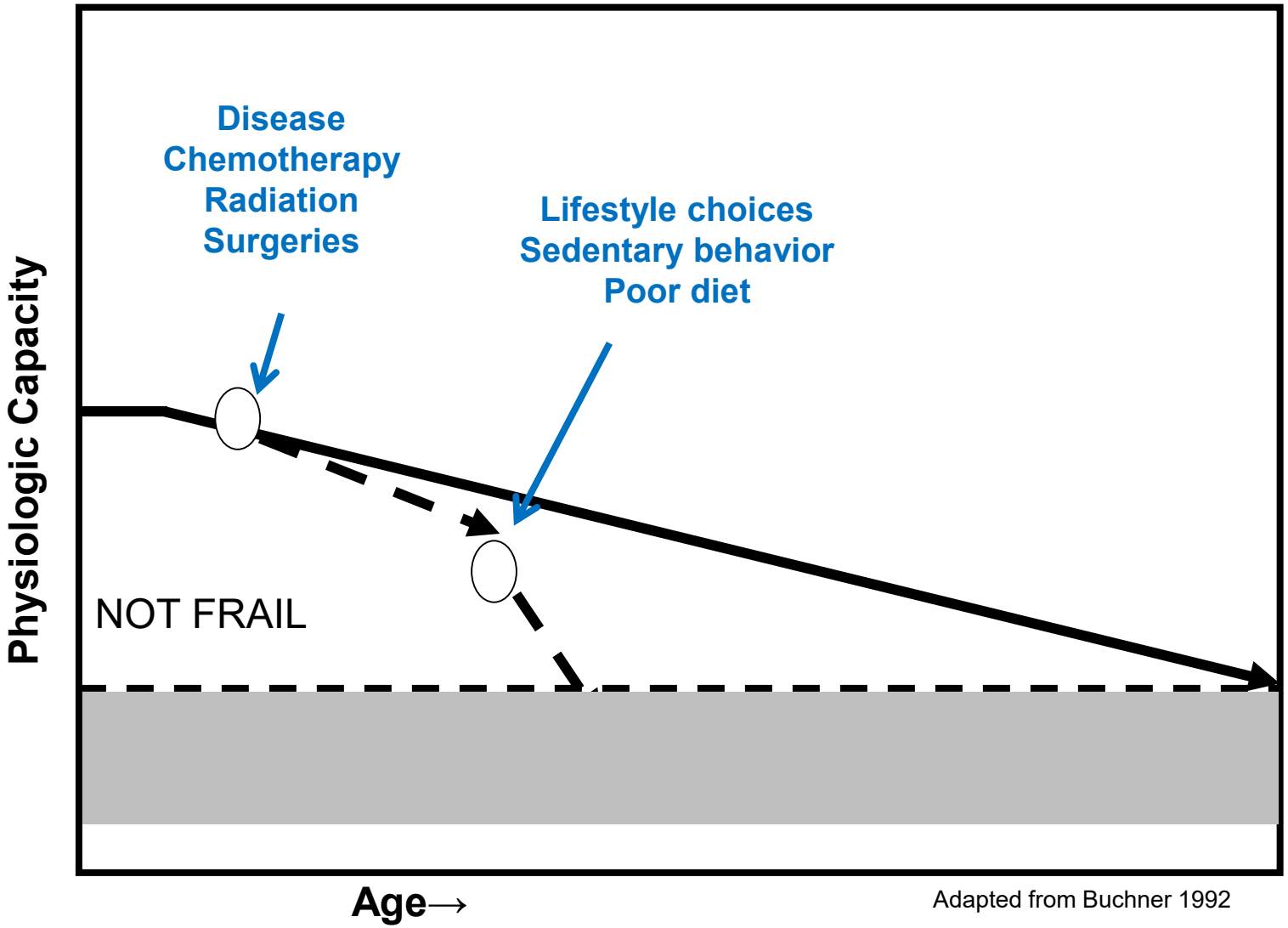
Adapted from Buchner 1992

Frailty and Exposures



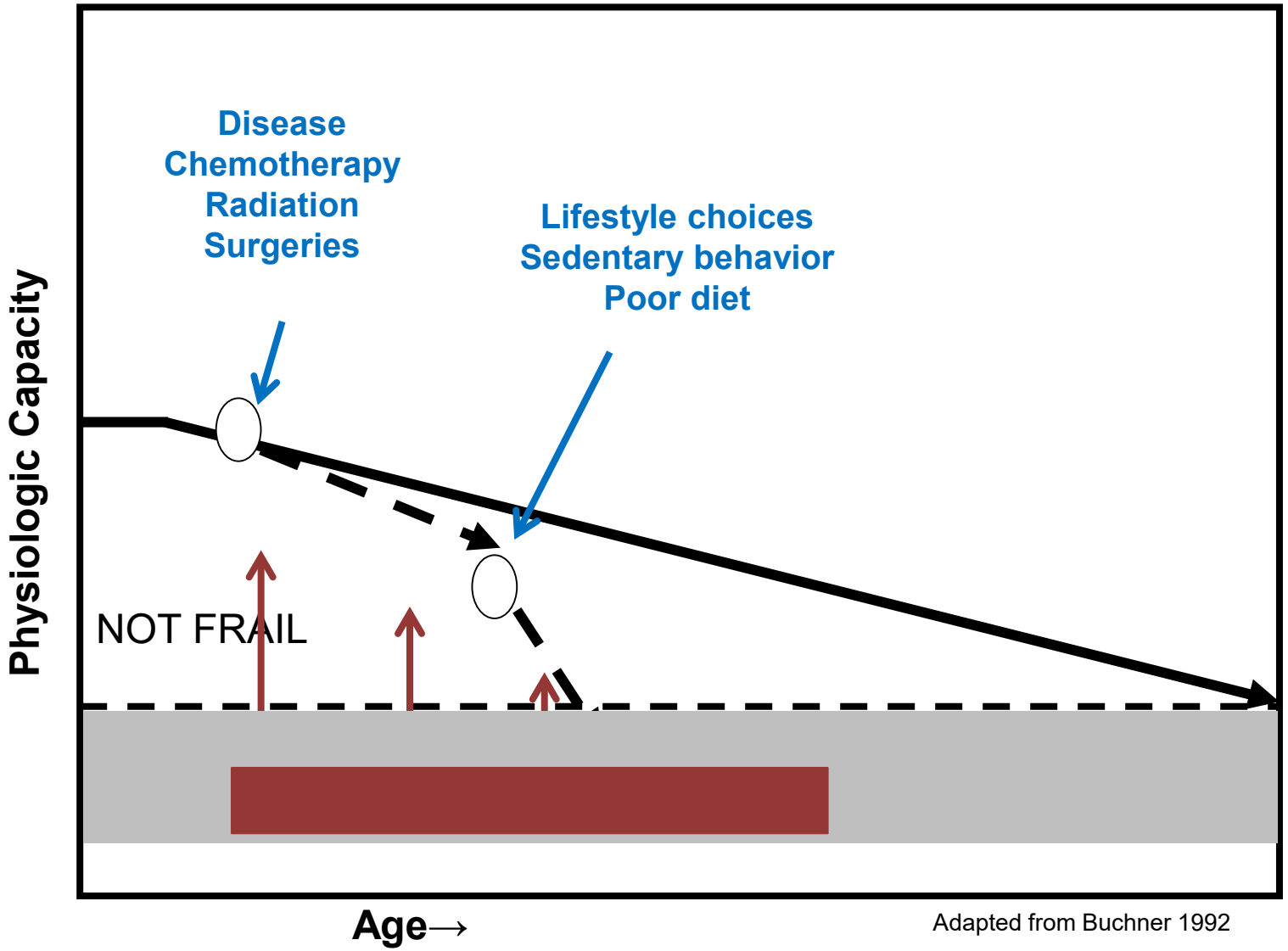
Adapted from Buchner 1992

Frailty and Lifestyle



Adapted from Buchner 1992

Frailty and Intervention



Adapted from Buchner 1992

Frailty in Childhood Cancer Survivors

VOLUME 31 · NUMBER 36 · DECEMBER 20 2013

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Physiologic Frailty As a Sign of Accelerated Aging Among Adult Survivors of Childhood Cancer: A Report From the St. Jude Lifetime Cohort Study

Kirsten K. Ness, Kevin R. Krull, Kendra E. Jones, Daniel A. Mulrooney, Gregory T. Armstrong, Daniel M. Green, Wassim Chemaitilly, Webb A. Smith, Carmen L. Wilson, Charles A. Sklar, Kyla Shelton, Deo Kumar Srivastava, Sabeen Ali, Leslie L. Robison, and Melissa M. Hudson

National Cancer Institute U01 CA195547

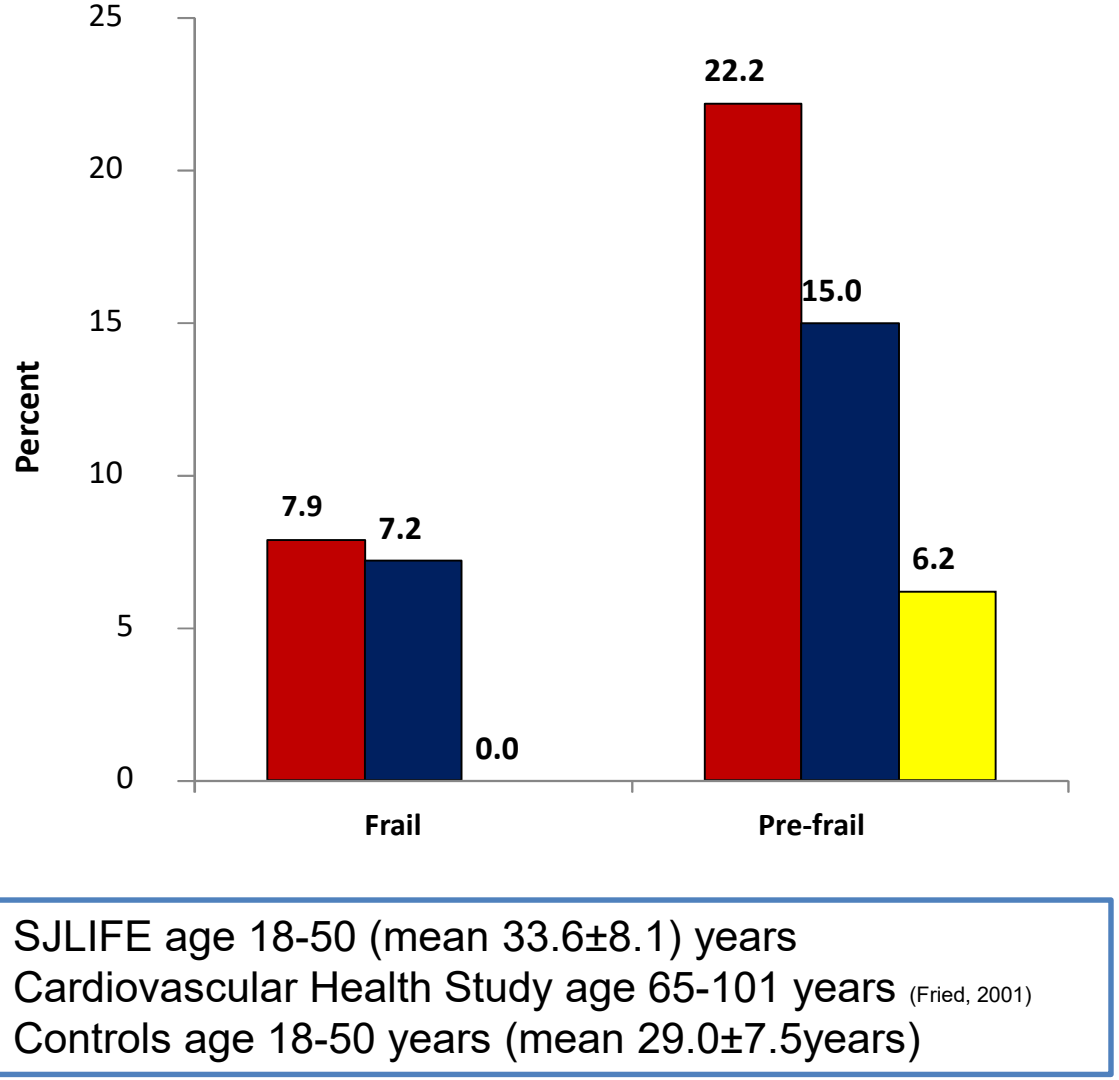
Fried Frailty Criteria

- Five components of fitness from the Cardiovascular Health Study (65-101 years of age)
  - –Muscle wasting
  - –Muscle weakness
  - –Self-reported exhaustion
  - –Slow walking speed
  - –Low energy expenditure
- Frail: ≥ 3 components
- Pre-frail: 2 components

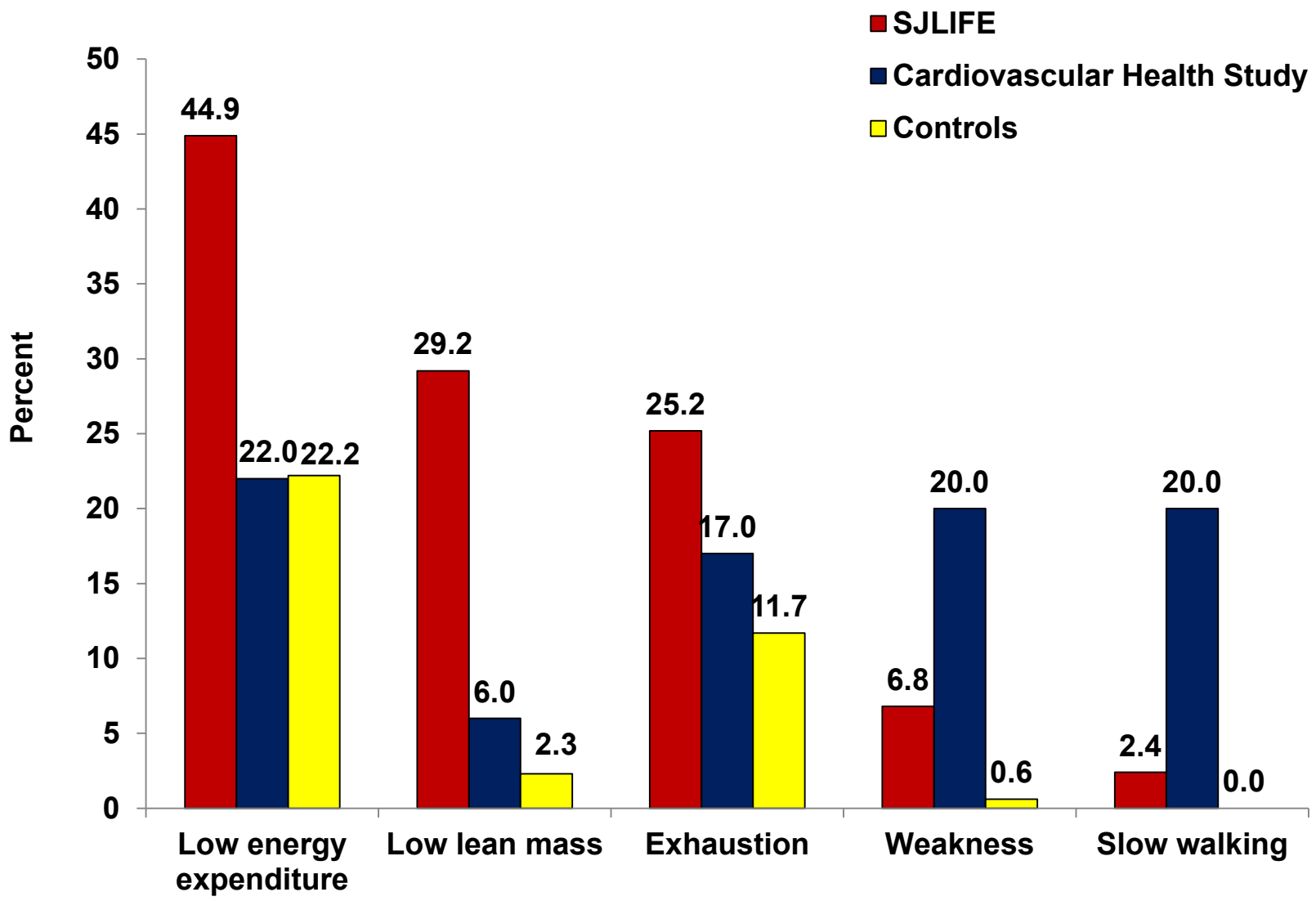
Fried 2001

Frailty in the St. Jude Lifetime Cohort (SJLIFE)

- N=1922 (50.3% male)
- Mean time since diagnosis 25.5±7.7 years
- Mean age at diagnosis 8.2±5.6 years
- 43% leukemia
- 33% with CRT



Prevalence of Frailty Components



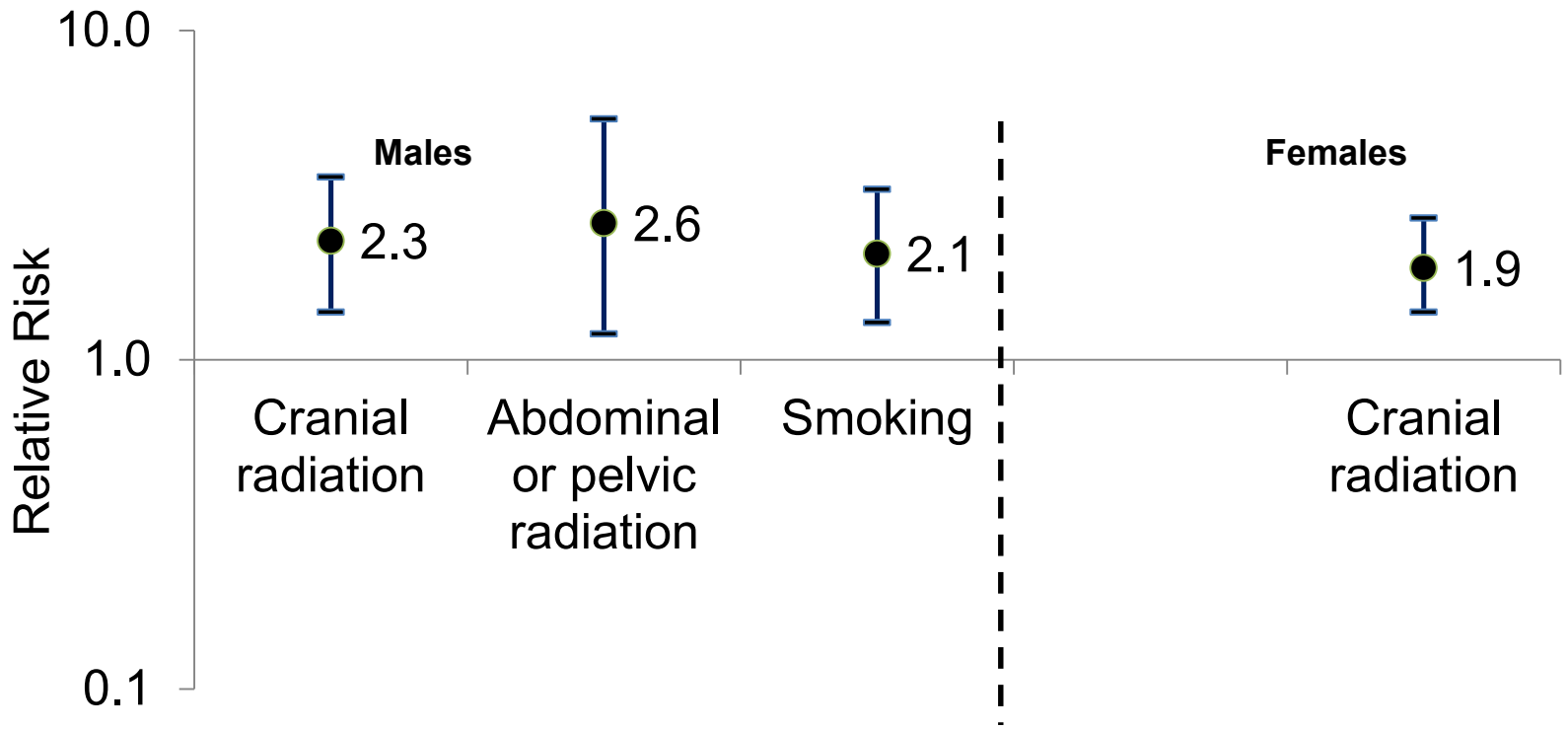
Frailty and Mortality

	Total		
Phenotype	N	Deaths	HR (95% CI)
Frailty	151	4.6%	2.6 (1.5-2.8)
No Frailty	1771	1.4%	

Adjusted for age and number of chronic medical conditions CTCAEv4.0 grade ≥ 3

Compares to adjusted HR in the Cardiovascular Health Study of 2.24 CI = (1.51-3.33)

Treatment and Relative Risk of Frailty



Adjusted for current age, age at diagnosis, chest radiation, doses of anthracycline, alkylating agents, glucocorticoids, platinum, vinca-alkaloids and methotrexate, duration of chemotherapy, alcohol intake, and body mass index

Validation of the Phenotype

J Clin Oncol, JCO01901266 2019 Dec 4 [Online ahead of print]

original reports

Prevalence and Predictors of Frailty in Childhood Cancer Survivors and Siblings: A Report From the Childhood Cancer Survivor Study

Samah Hayek, DrPH[1]; Todd M. Gibson, PhD[1]; Wendy M. Leisenring, ScD[2]; Jennifer L. Guida, PhD[3]; Maria Monica Gramatges, MD, PhD[4]; Philip J. Lupo, PhD, MPH[4]; Rebecca M. Howell, PhD[5]; Kevin C. Oeffinger, MD[6]; Smita Bhatia, MD, MPH[7]; Kim Edelstein, PhD[8]; Melissa M. Hudson, MD[1]; Leslie L. Robison, PhD[1]; Paul C. Nathan, MD, MSc[9]; Yutaka Yasui, PhD[1]; Kevin R. Krull, PhD[1]; Gregory T. Armstrong, MD, MSCE[1]; and Kirsten K. Ness, MPH, PhD[1]

Participants

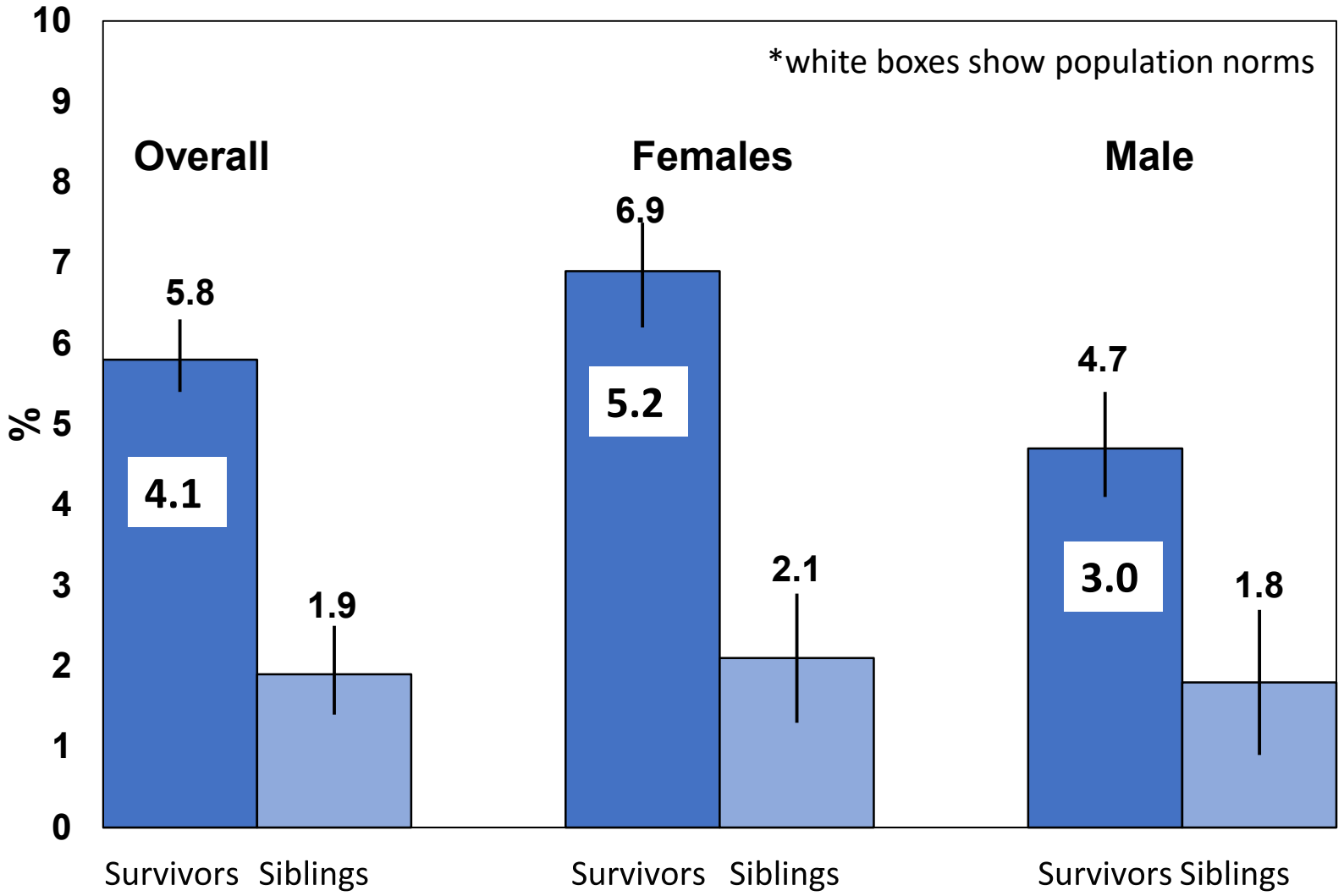
- Participants were 10,899 members of the Childhood Cancer Survivor Study (CCSS) ≥ age 18 years and alive at the end of follow-up.
- Retrospective cohort was funded in 1994
- CCSS includes 5-year survivors diagnosed with cancer prior age 21, between 1970-1999, and their siblings
- 31 contributing centers in North America
- Eight common pediatric cancer types

Self-Report Definition

Frailty was characterized as ≥ 3 of the following self-reported conditions:

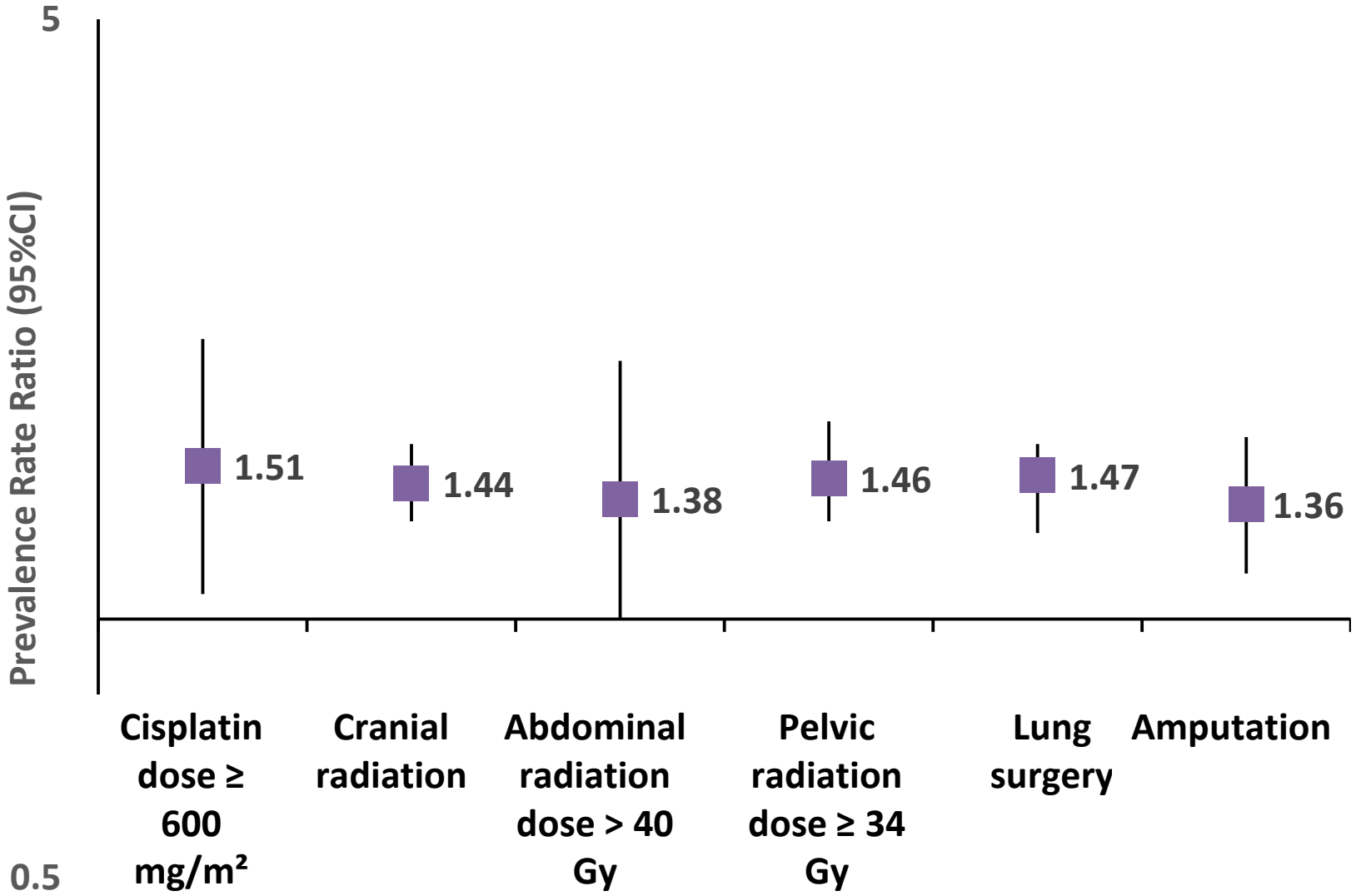
Component	*Definition*
Low lean mass	BMI <18.5 kg/m² or unintentional weight loss ≥10 lbs in past year
Self-reported exhaustion	Score ≤40 on vitality subscale of Short-Form 36
Low energy expenditure (LEE)	Activity levels captured by NHANES physical activity questionnaire, defined as <383 kcal/wk males, <270 kcal/wk females
Slow walking speed	Limited >3 months in past 2 years walking one block, walking uphill, or climbing a few flights of stairs.
Weakness	Weakness or inability to move arms

Age-adjusted Prevalence of Frailty by Sex

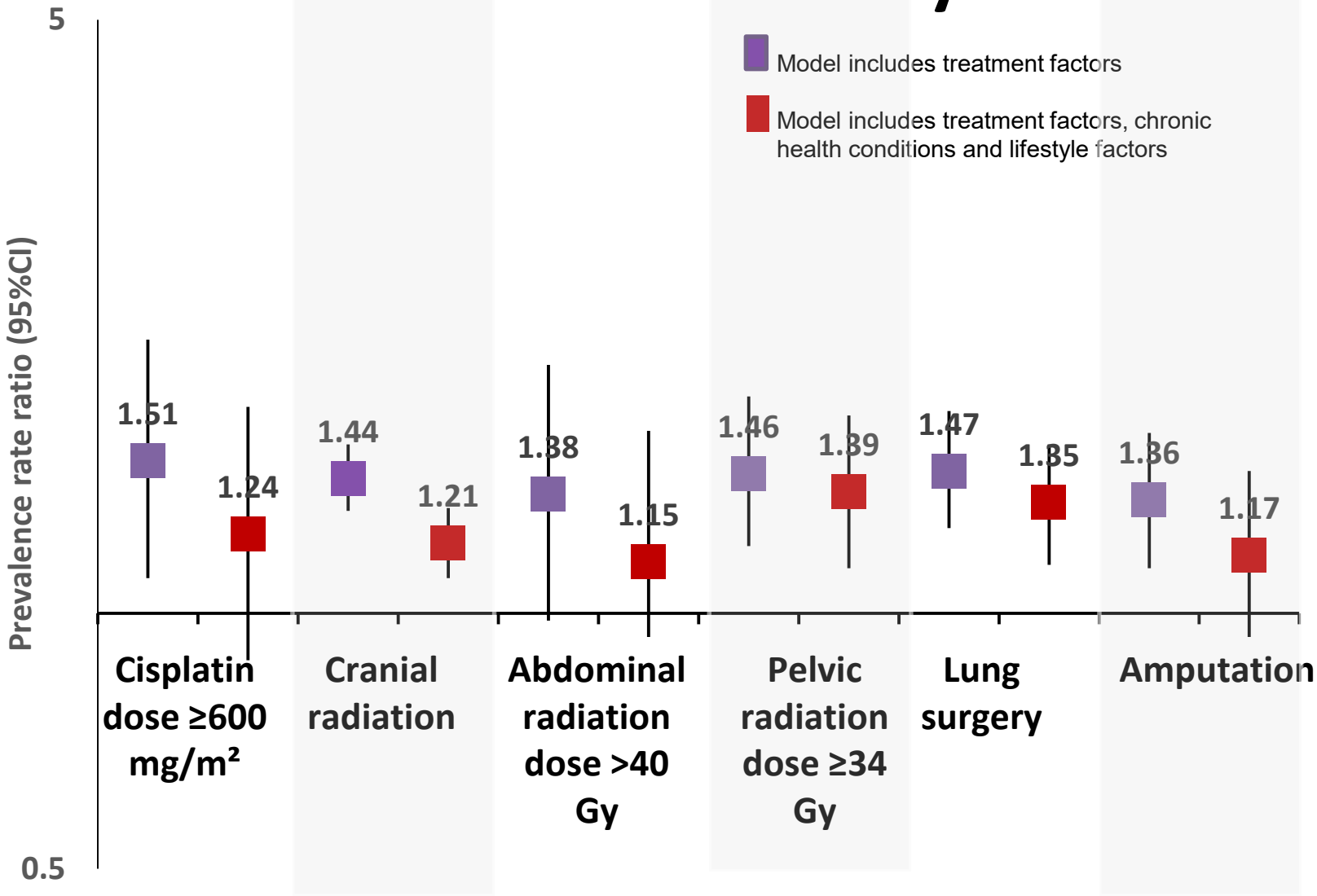


Eggiman et al. Journal of Gerontology: Medical science 2009

Treatment Exposures and Frailty



Treatment Exposures and Frailty, Adjusted for Grade 3-4 Chronic Conditions & Lifestyle



Progression of Frailty in the SJLIFE Cohort

Baseline St. Jude Life Assessment

- Treated at St. Jude Children's Research Hospital
- 10 year survivor
- 18-45 years of age (median 30)
- 2008-2013

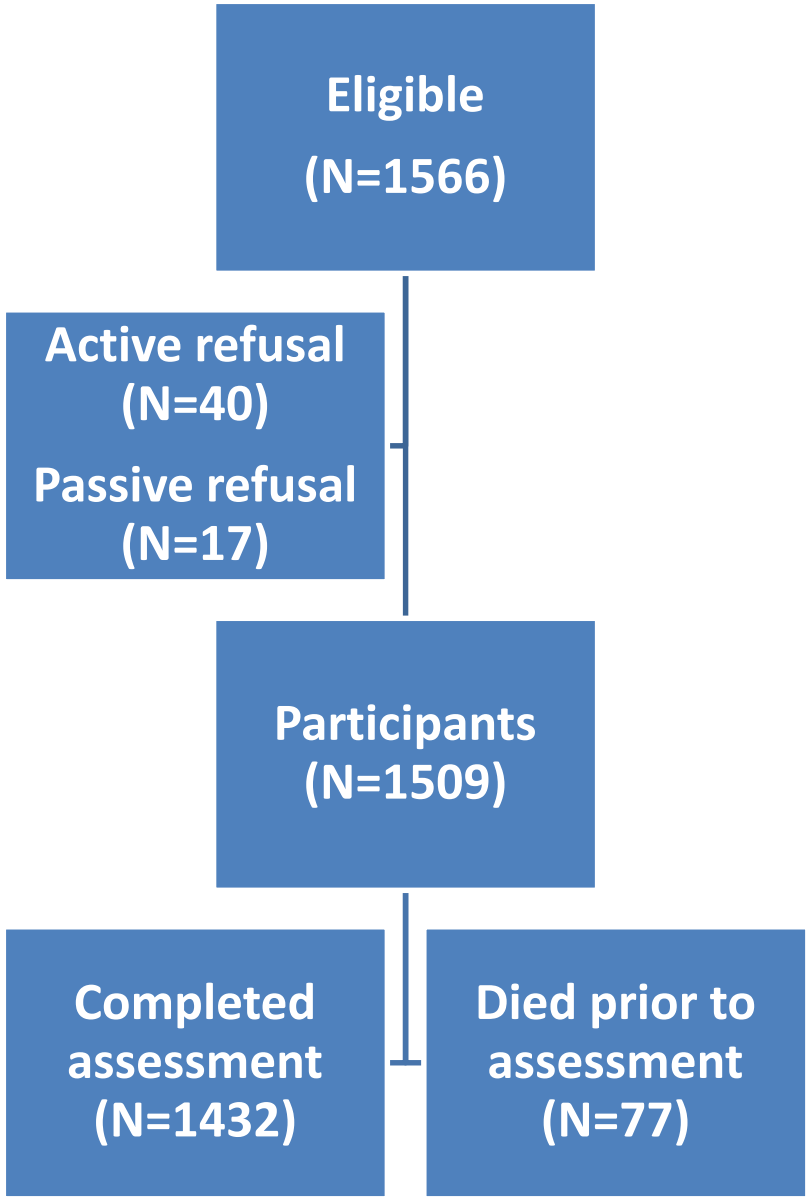
4 - 6 years

Follow-up Assessment

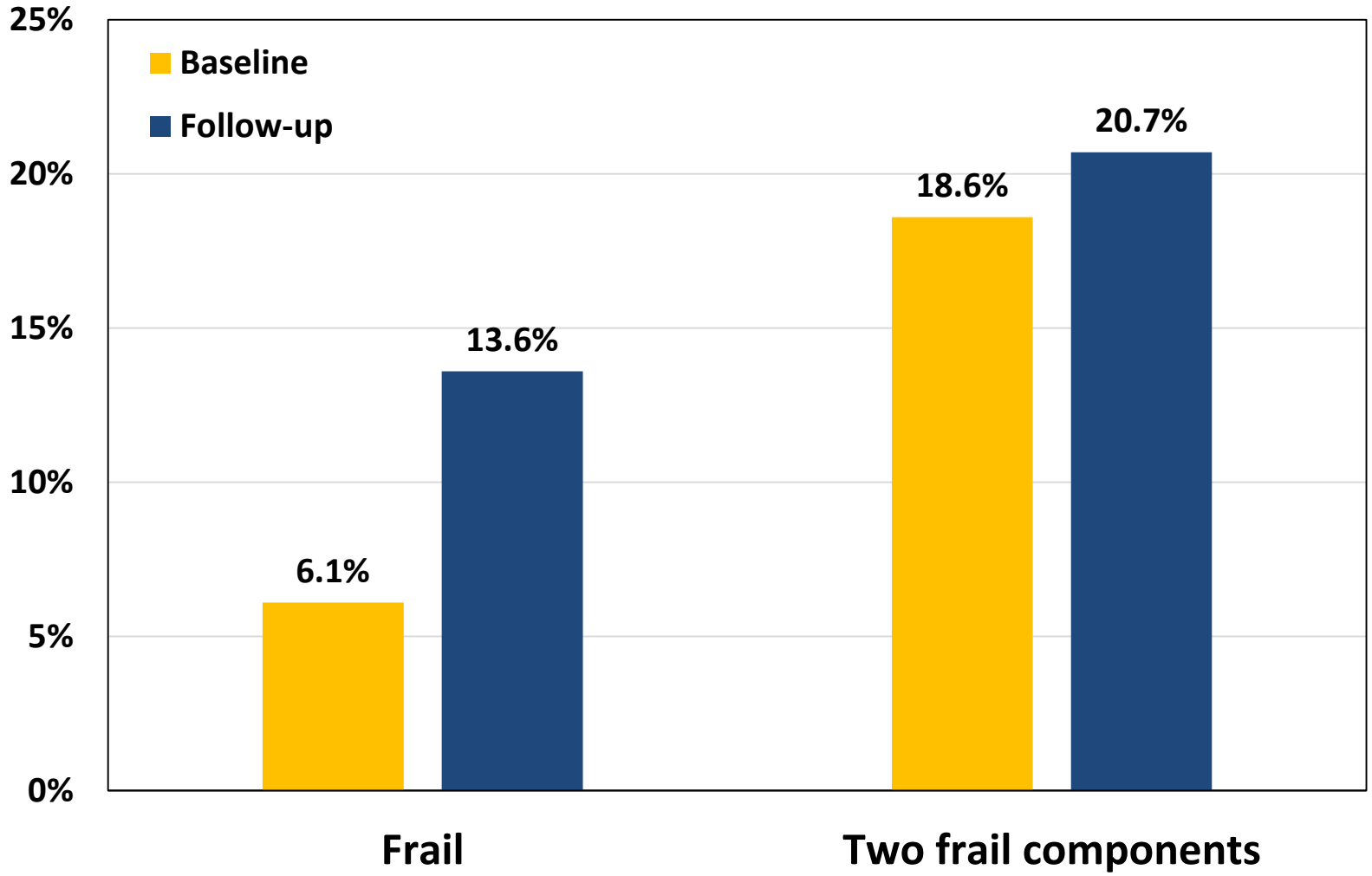
- 2013-2018

Participants

- 0-22 years old at diagnosis (median 7)
- 51.6% male
- 16.1% non-white
- 37.9% leukemia
- 19.5% lymphoma
- 10.9% CNS tumor
- 11.0% sarcoma
- 7.2% Wilms tumor
- 4.4% neuroblastoma
- 3.3% retinoblastoma
- 5.8% other



Prevalence of Frailty & Components



all $p < 0.001$*

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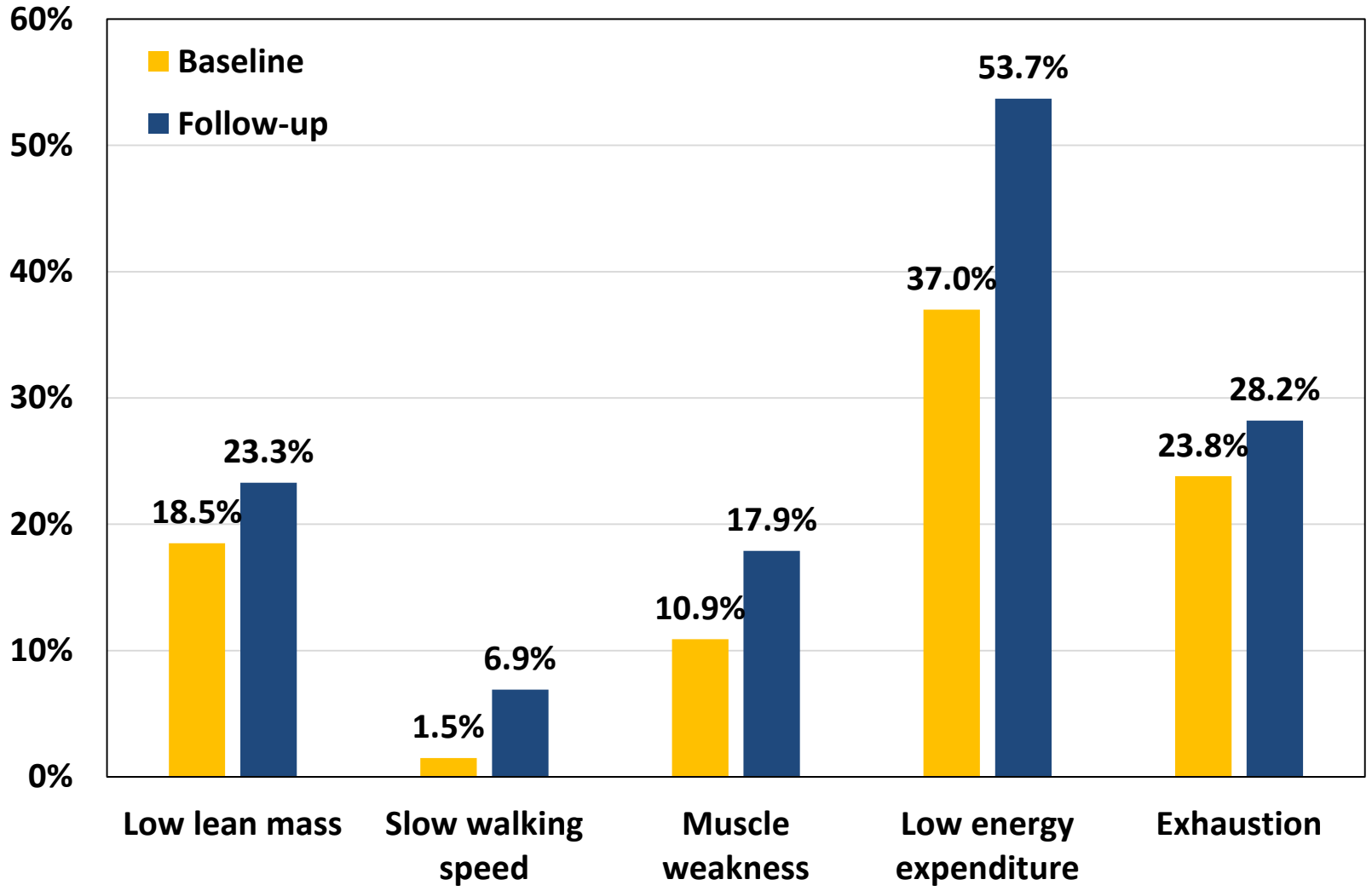


all $p < 0.001$*

Risk for Death by Frailty Status

	Hazard ratio	95% CI
Frailty	3.53	1.95-6.38
Age (1-year increments)	1.06	1.03-1.10
Female	0.64	0.40-1.02
Non-white race	0.88	0.45-1.73
Cardiac condition	1.97	1.19-3.26
Pulmonary condition	2.32	1.38-3.89
Neurological condition	1.91	1.14-3.22
Endocrine condition	2.59	1.48-4.54

There were 77 deaths in the cohort, 17.4% among those who were frail and 4.3% among those who were not frail.

Specific Targets for Intervention

Published online October 22, 2019

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

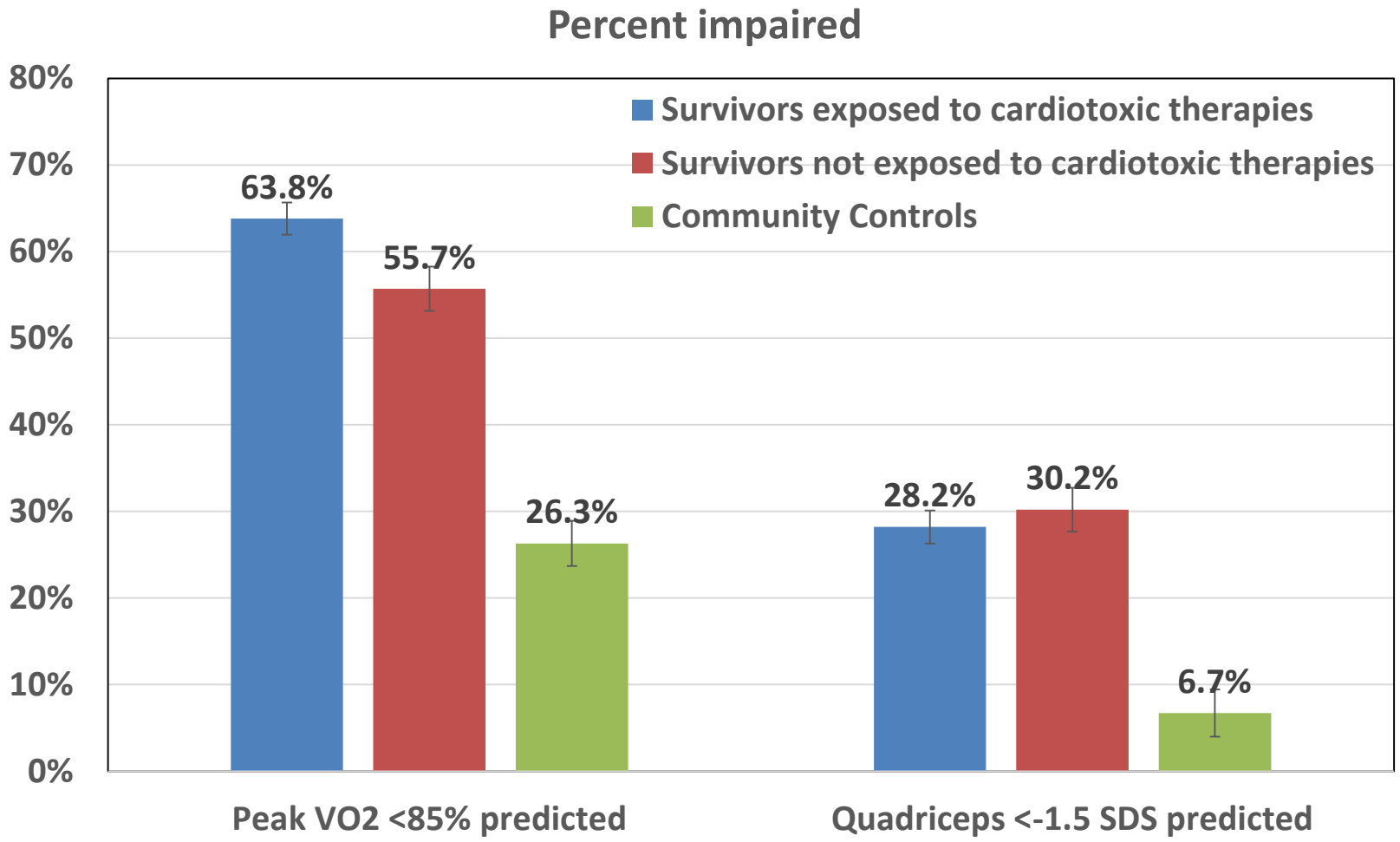
original reports

Exercise Intolerance, Mortality, and Organ System Impairment in Adult Survivors of Childhood Cancer

Kirsten K. Ness, PhD[1]; Juan C. Plana, MD[2]; Vijaya M. Joshi, MD[3]; Russell V. Luepker, MD[4]; Jean B. Durand, MD[5]; Daniel M. Green, MD[1]; Robyn E. Partin, MS[1]; Aimee K. Santucci, PhD[1]; Rebecca M. Howell, PhD[5]; Deo Kumar Srivastava, PhD[1]; Melissa M. Hudson, MD[1]; Leslie L. Robison, PhD[1]; and Gregory T. Armstrong, MD[1]

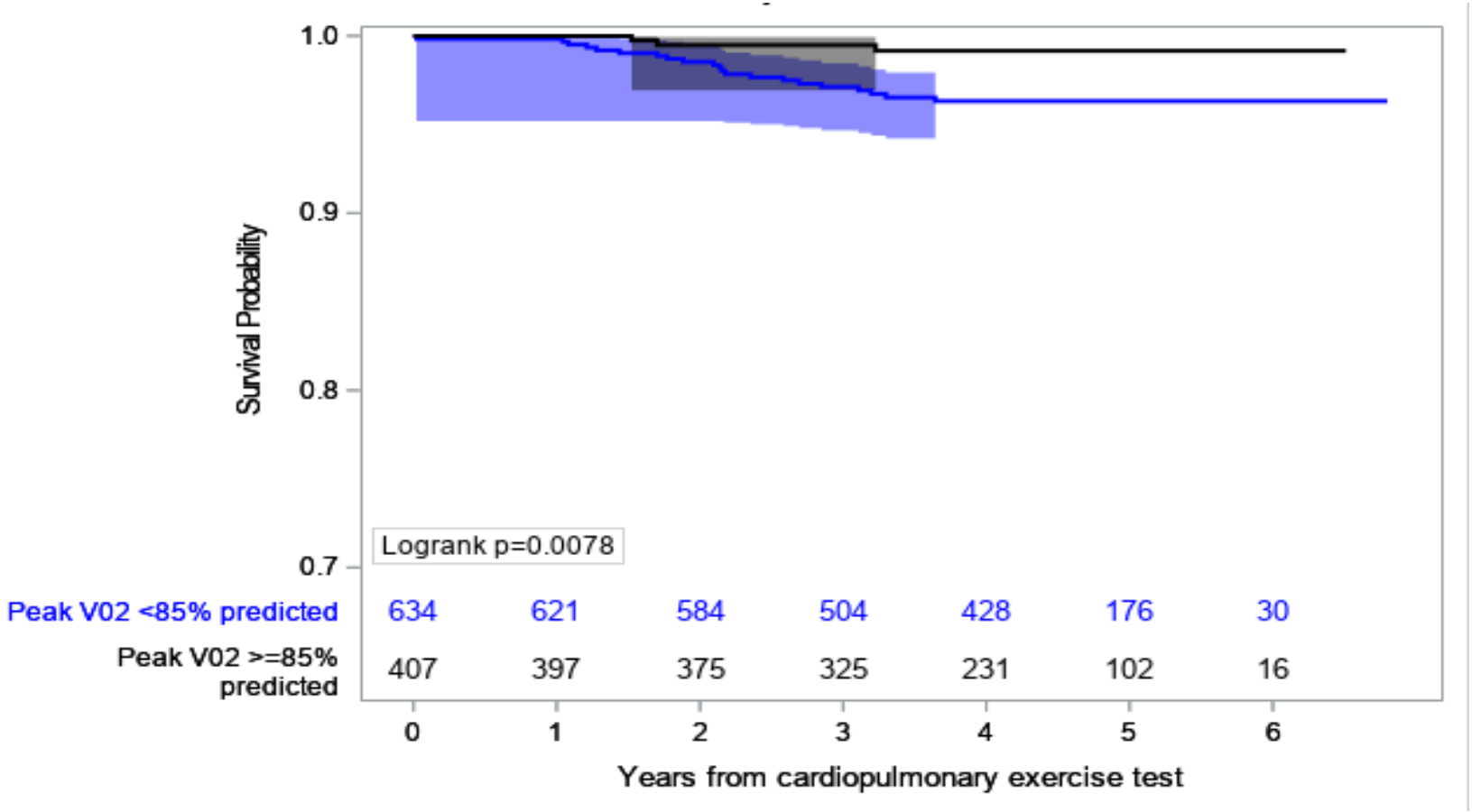
National Cancer Institute R01 CA157838

Specific Targets for Intervention



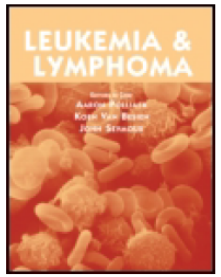
1041 survivors, mean age 35±9 years (666 exposed to anthracyclines±chest radiation), 275 community controls (mean age 34±10 years) participated in CPET and strength testing

Association Between Exercise Tolerance and Mortality



After a median follow-up of 4 years, there were 24 survivor deaths, 21 (3.3%) among those with and 3 among those without exercise intolerance (Adjusted HR 3.93 (95% CI 1.09-14.14) comparing those with to those without, exercise intolerance.

Physiologic Impairments Start Early



Leukemia & Lymphoma

Taylor & Francis
Taylor & Francis Group

Leuk Lymphoma 2015 Apr;56(4):1004-11

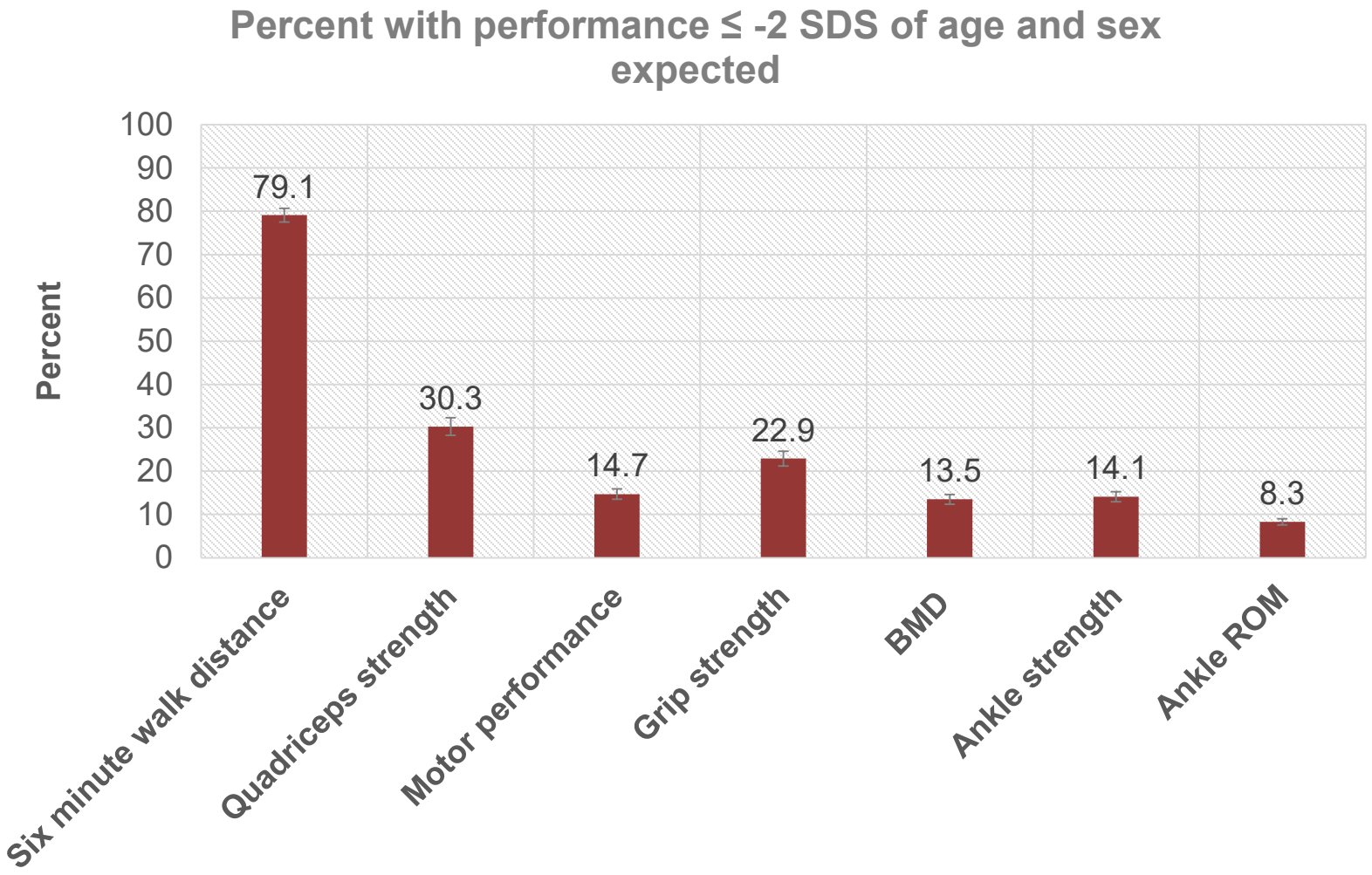
ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: http://www.tandfonline.com/loi/ilal20

Skeletal, neuromuscular and fitness impairments among children with newly diagnosed acute lymphoblastic leukemia

Kirsten K. Ness, Sue C. Kaste, Liang Zhu, Ching-Hon Pui, Sima Jeha, Paul C. Nathan, Hiroto Inaba, Karen Wasilewski-Masker, Durga Shah, Robert J. Wells, Robyn E. Karlage, Leslie L. Robison & Cheryl L. Cox

National Cancer Institute R01CA129384

Physiologic Impairments Start Early



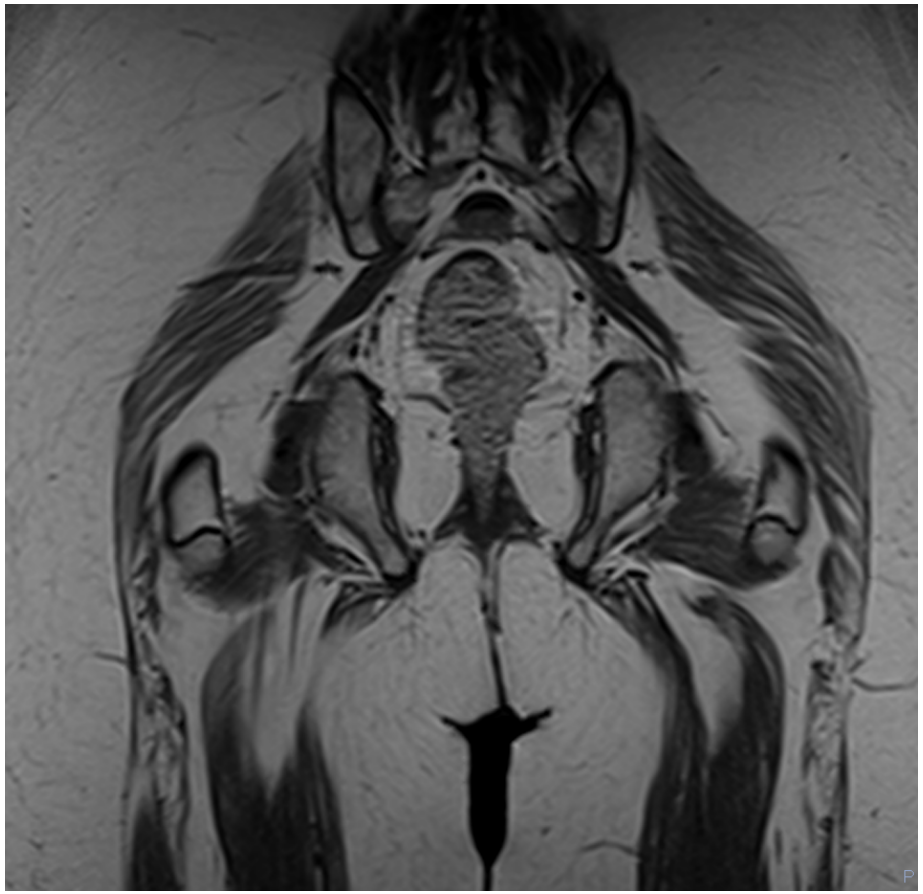
109 children with newly diagnosed ALL, median age 10 (4-18 years), 65.1% male, 63.3% non-Hispanic white

Proximal Strength in Children with Newly Diagnosed ALL

	ALL survivors		Population controls	
Quadriceps (Newtons)	201.9	(8.3)	236.1	(5.4)

Proximal muscular strength impaired among 109 children with newly diagnosed ALL (7-10 days after dx) – treated on Total XVI or ALL0932 (median age 10 (range 4-18) years)

Example of Fatty Infiltration of Proximal Muscle



12 year old male during maintenance therapy for T-cell leukemia

Impairments Often Persist

Cancer

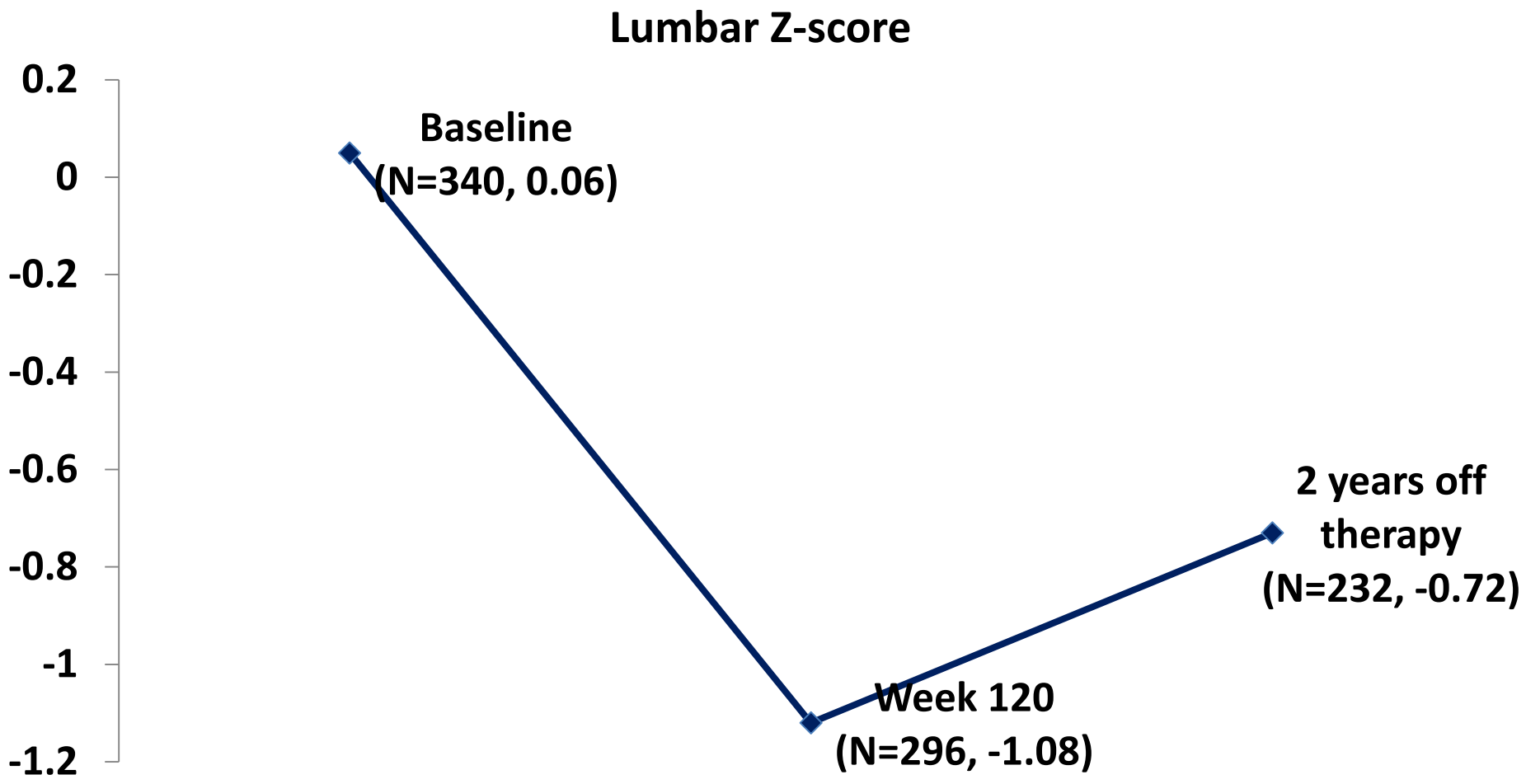
2017 Mar;124(5)1025-35

Original Article

Bone Mineral Density in Children With Acute Lymphoblastic Leukemia

Hiroto Inaba, MD, PhD[1,2]; Xueyuan Cao, PhD[3,4]; Alice Q. Han, BA[1]; John C. Panetta, PhD[5]; Kirsten K. Ness, PhD[6]; Monika L. Metzger, MD[1,2]; Jeffrey E. Rubnitz, MD, PhD[1,2]; Raul C. Ribeiro, MD[1,2]; John T. Sandlund, MD[1,2]; Sima Jeha, MD[1,2]; Cheng Cheng, PhD[3]; Ching-Hon Pui, MD[1,2]; Mary V. Relling, PharmD[5,7]; and Sue C. Kaste, DO[8,9]

Bone Loss During ALL Therapy



Inaba 2018

Lifestyle is Important

Journal of the American Physical Therapy Association

Physical Therapy

Dietary Protein Intake and Lean Muscle Mass in Survivors of Childhood Acute Lymphoblastic Leukemia: Report From the St. Jude Lifetime Cohort Study

Alexandra M. Boland, Todd M. Gibson, Lu Lu, Sue C. Kaste, James P. DeLany, Robyn E. Partin, Jennifer Q. Lanctot, Carrie R. Howell, Heather H. Nelson, Wassim Chemaitilly, Ching-Hon Pui, Leslie L. Robison, Daniel A. Mulrooney, Melissa M. Hudson, Kirsten K. Ness

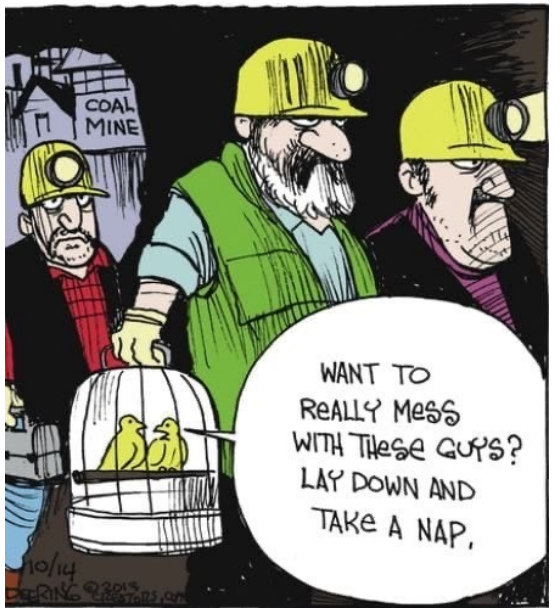
Physical Therapy, Volume 96, Issue 7, 1 July 2016, Pages 1029–1038

National Cancer Institute R01 CA132901

Lean Muscle Mass in ALL Survivors

Conclusions

- Childhood cancer survivors demonstrate an aging phenotype.
- Specific targets for intervention exist.
- Mechanistic studies may reveal new targets for intervention.
- In the meantime, interventions are underway across the childhood cancer survivor continuum.



Next Steps

- Continue investigations to better understand the pathobiology of this aging phenotype.
- Evaluate the contributions of lifestyle to the pathobiology of aging.
- Design and test interventions to address multiple components of the aging phenotype.
- Design dissemination mechanisms for studies with positive results.

Biological indicators and molecular mechanisms of premature, accelerated aging in survivors of childhood cancer

M. Monica Gramatges, MD, PhD

Associate Professor of Pediatrics

Texas Children's Cancer and Hematology Centers, Dan L. Duncan Comprehensive Cancer Center

Baylor College of Medicine

January 14, 2020

Objectives

- Review hallmarks of physiologic aging
- Review the current understanding of molecular mechanisms underlying premature aging in survivor populations
- Discuss the potential impact of chemotherapy and radiation on general and organ-specific aging
- Suggest opportunities for therapeutic intervention
- Provide considerations for proposals-in-development that include aims investigating aging-related biomarkers

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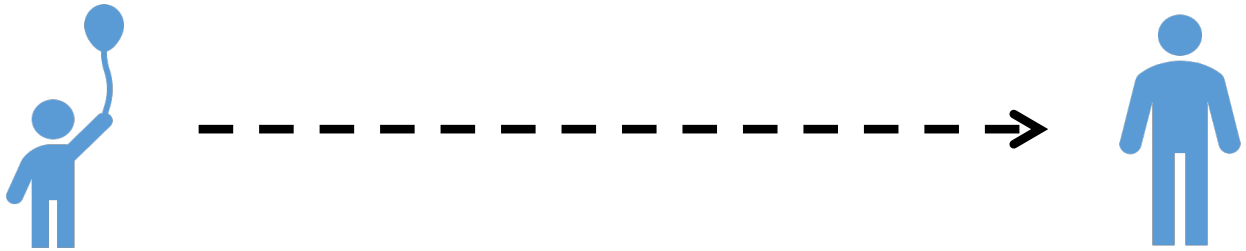
Risks for late effects are determined by treatment exposure and dose, and further influenced by demographics, behavioral and lifestyle choices, and genetic factors



Children's Oncology Group Long Term Follow Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, v.5.0
http://www.survivorshipguidelines.org//default.htm

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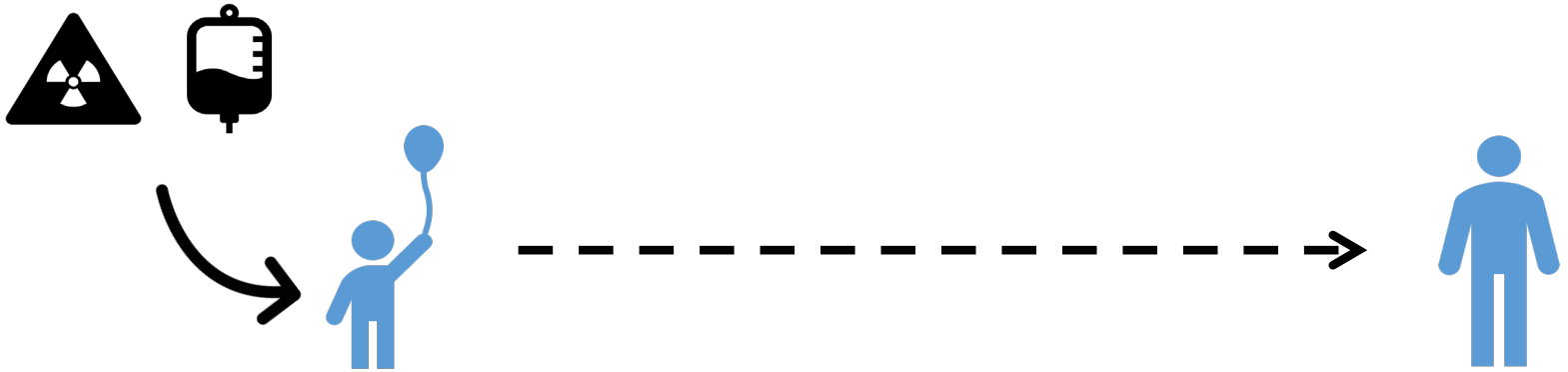

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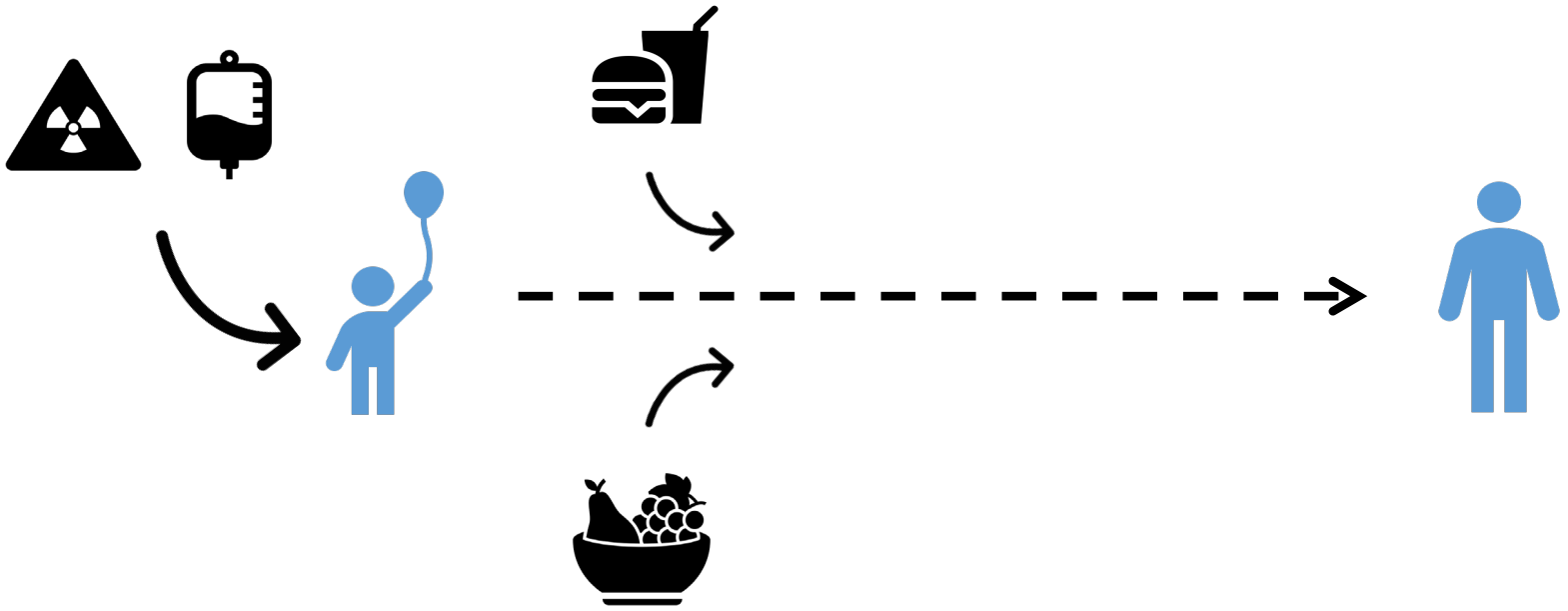

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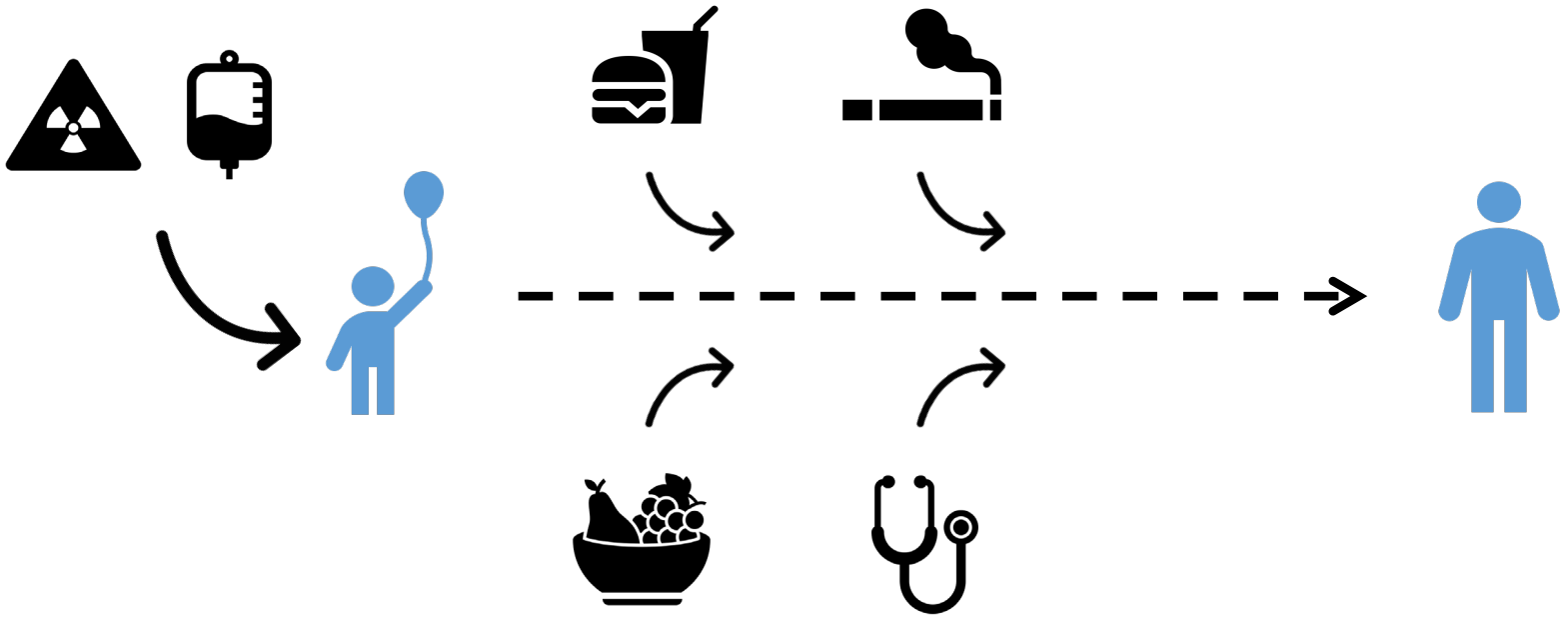

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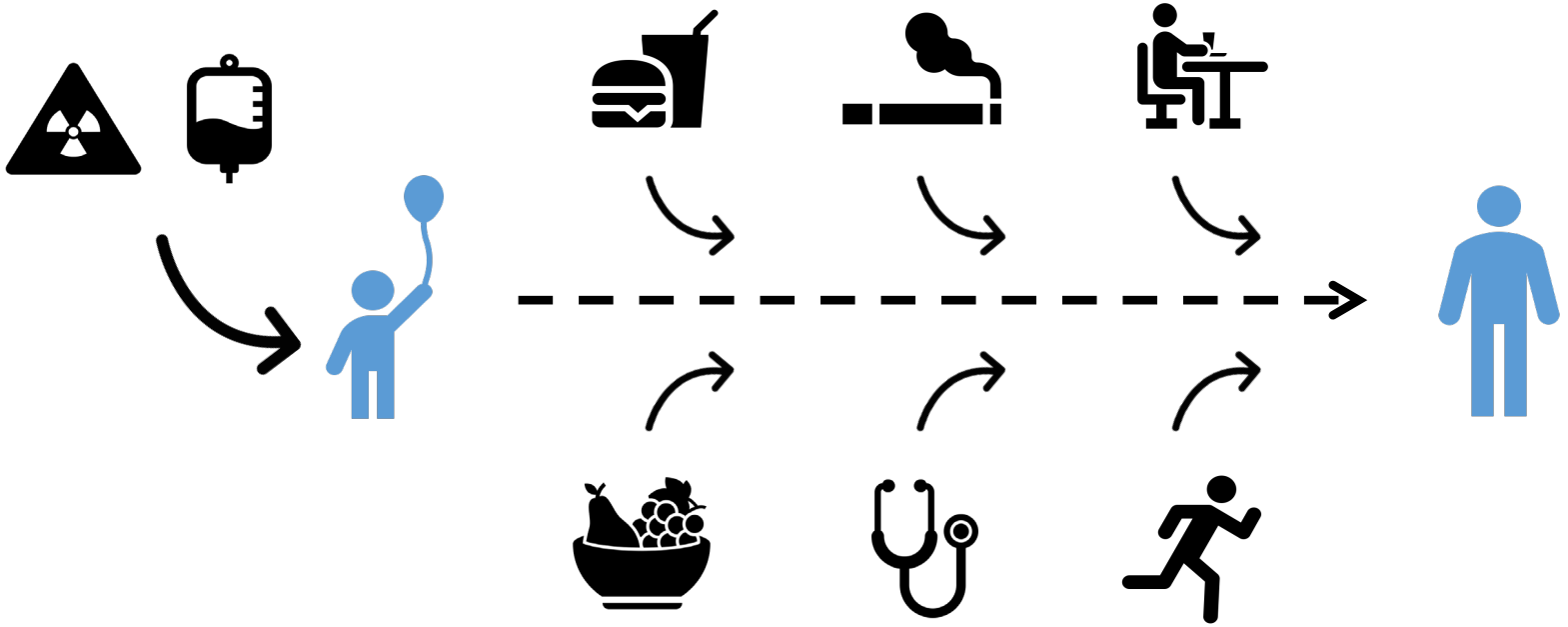

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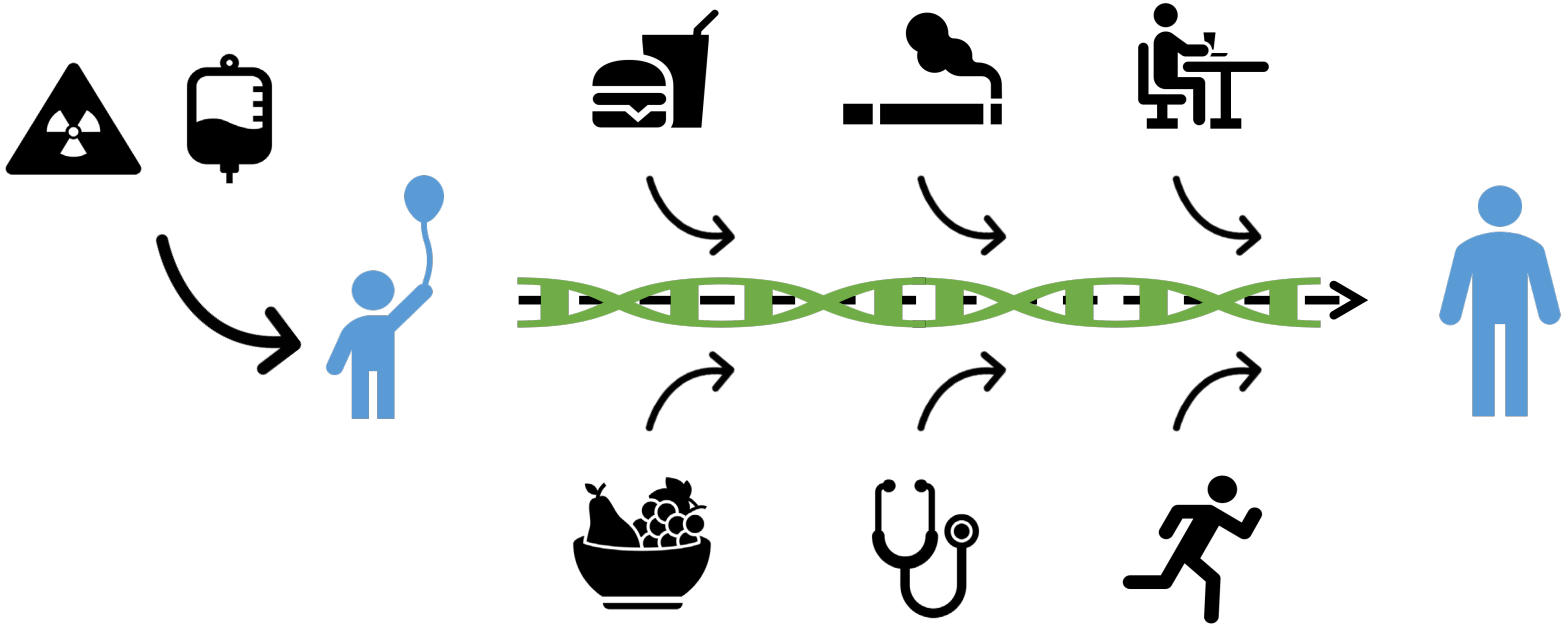

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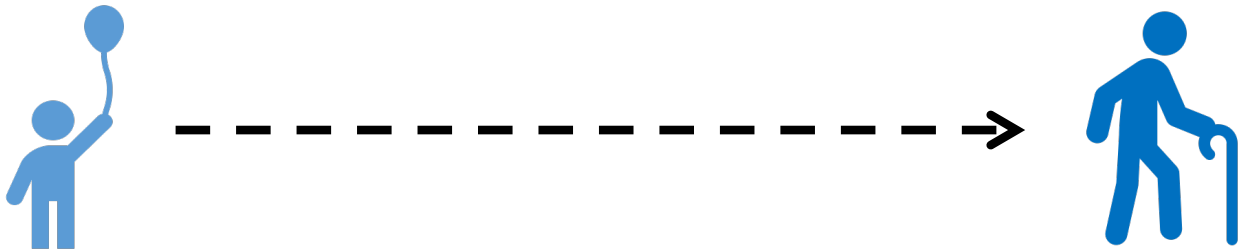
Chronic health conditions resulting from the accumulation of late effects over time, excess risk of frailty, and limitations in physical performance, together suggest that childhood cancer diagnosis and treatment augment risk for premature, accelerated aging in survivors



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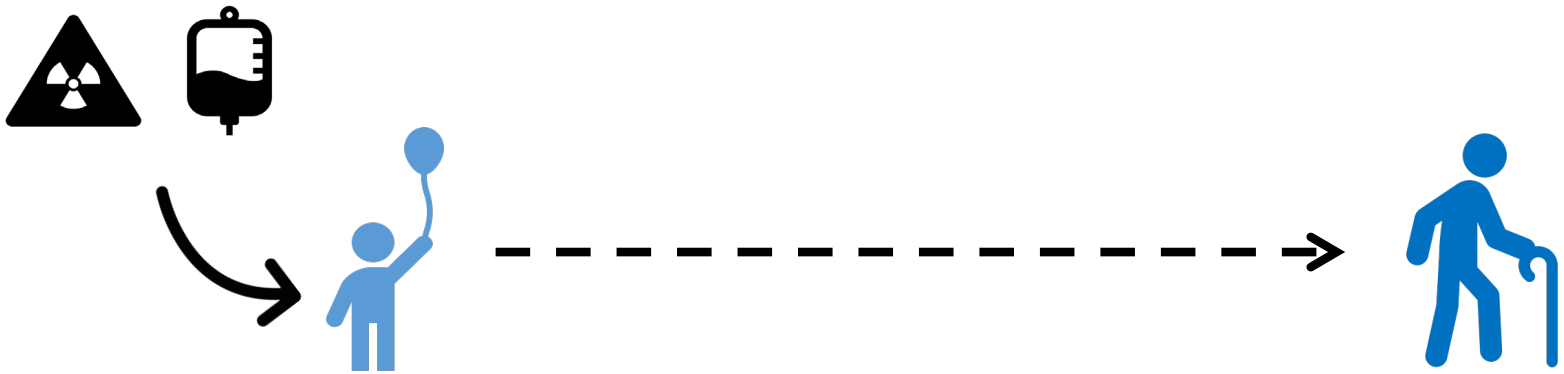

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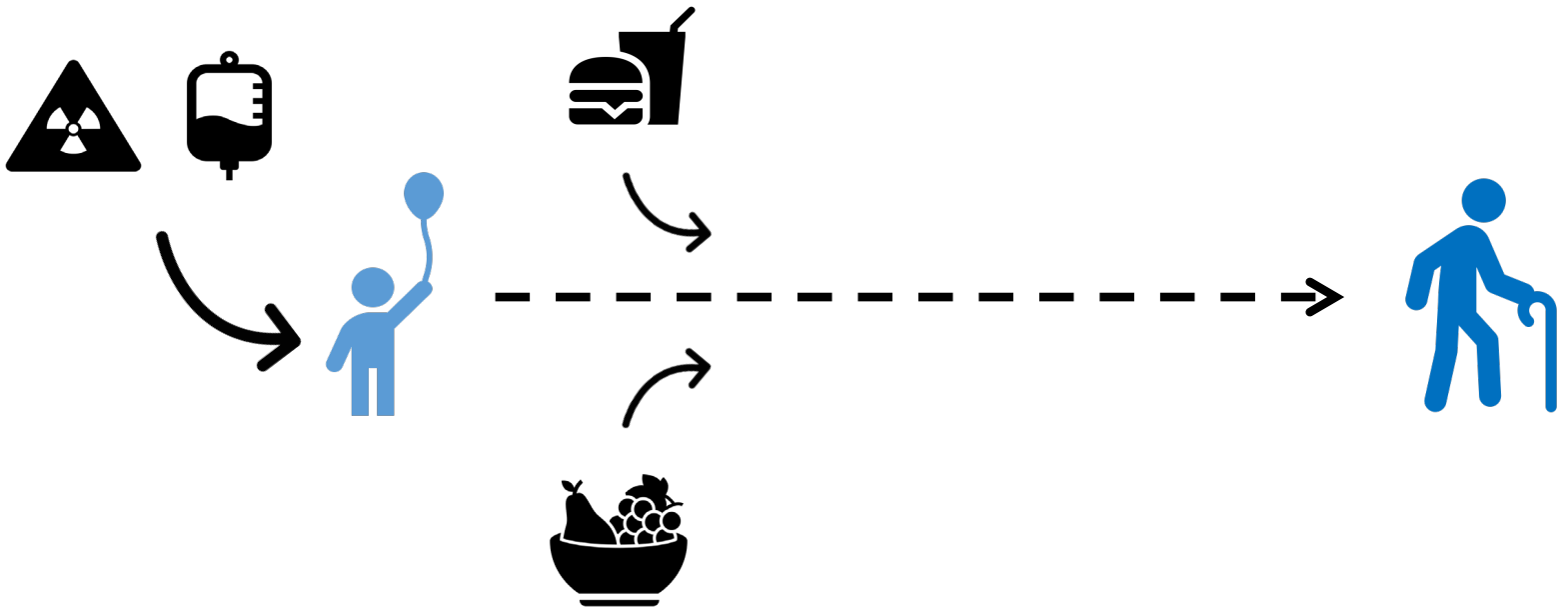

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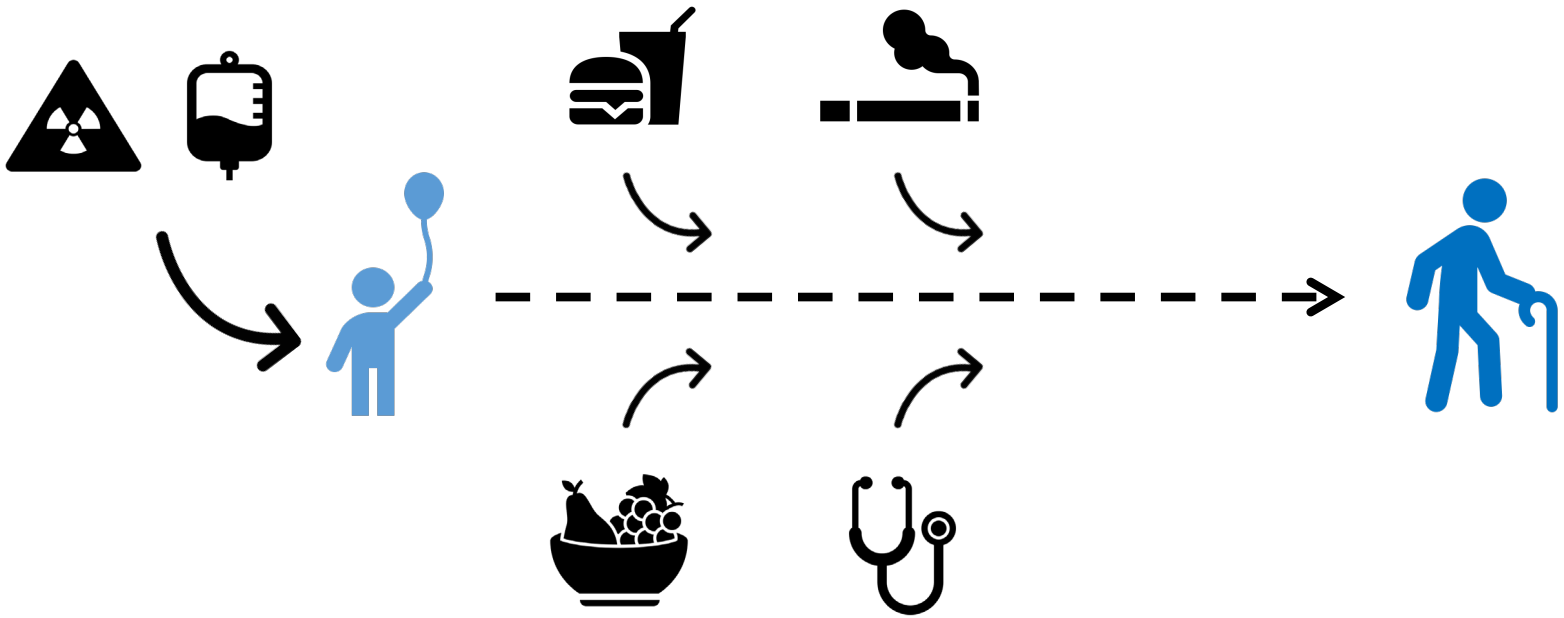

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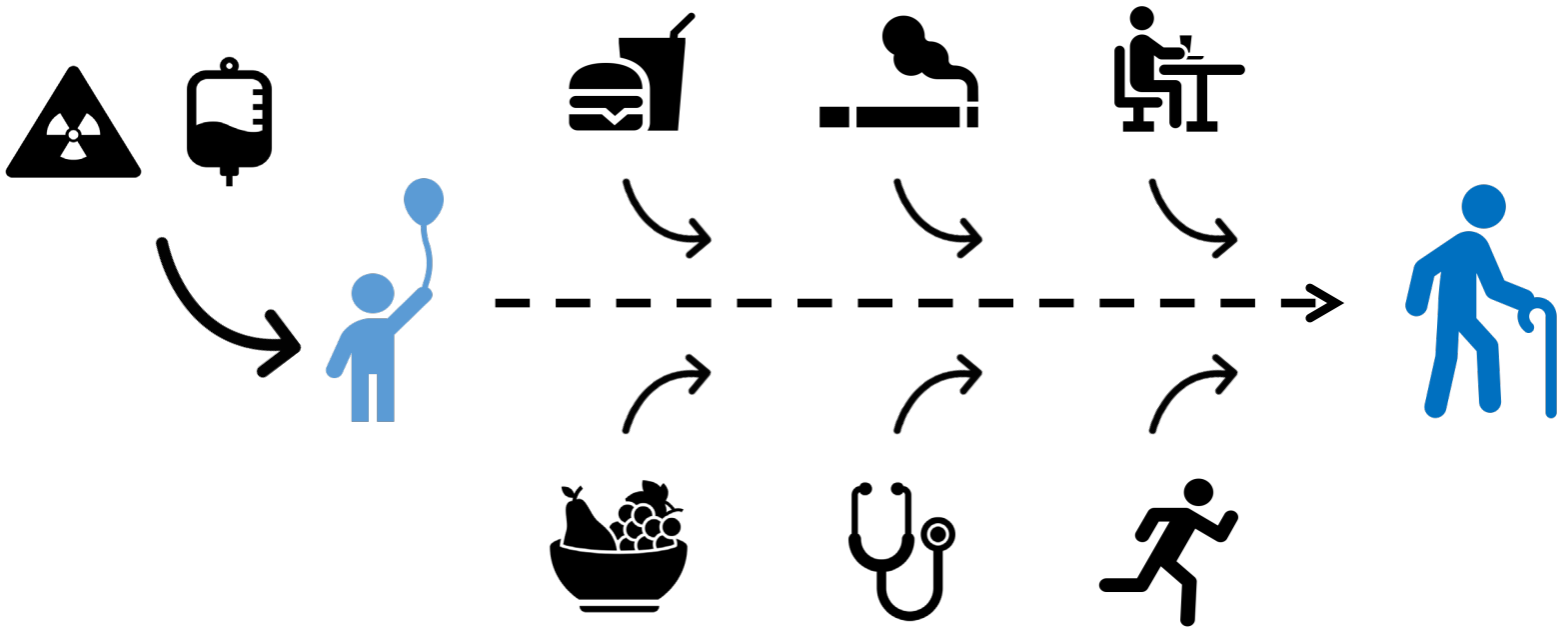

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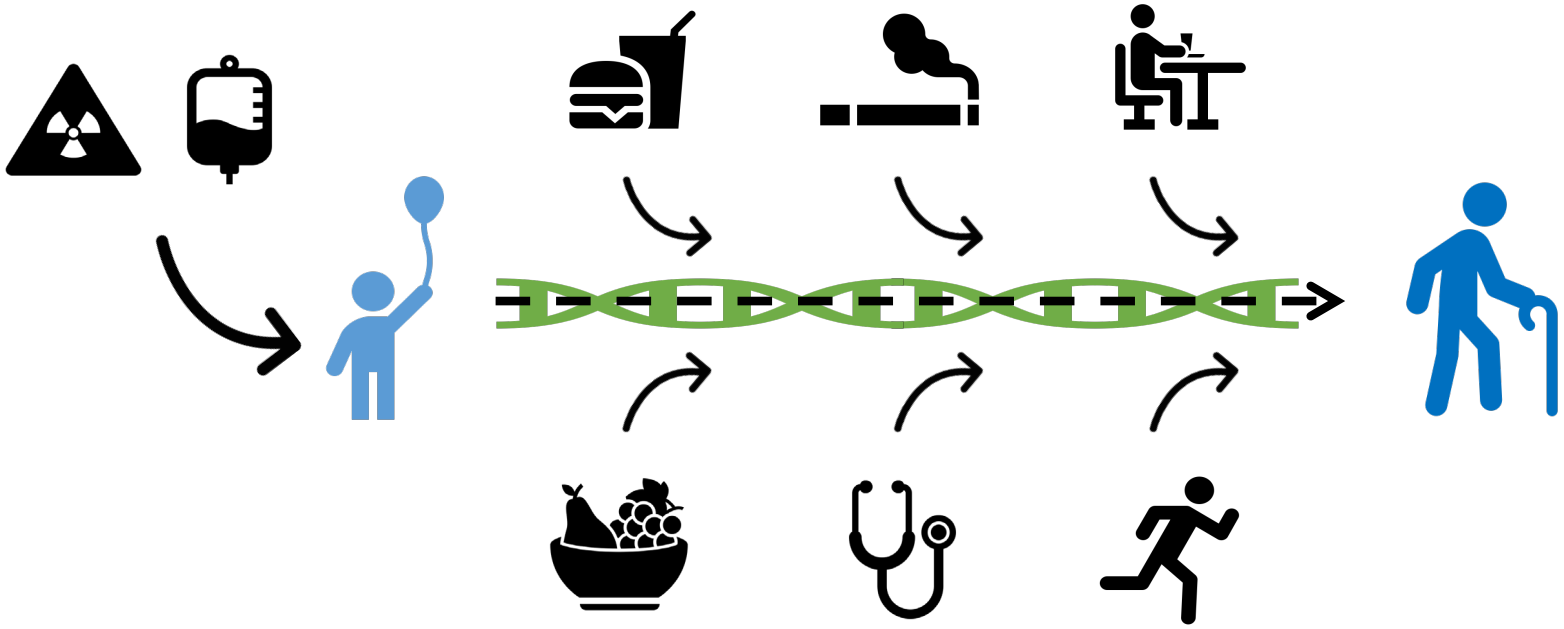

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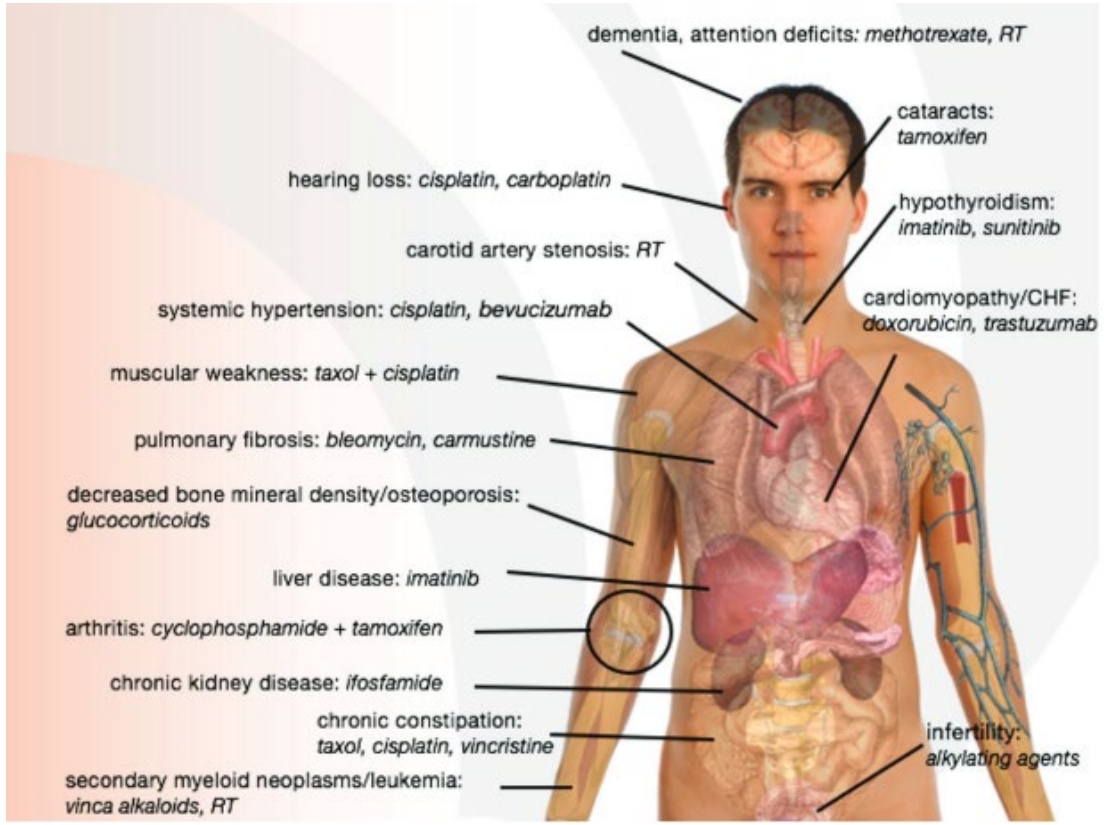
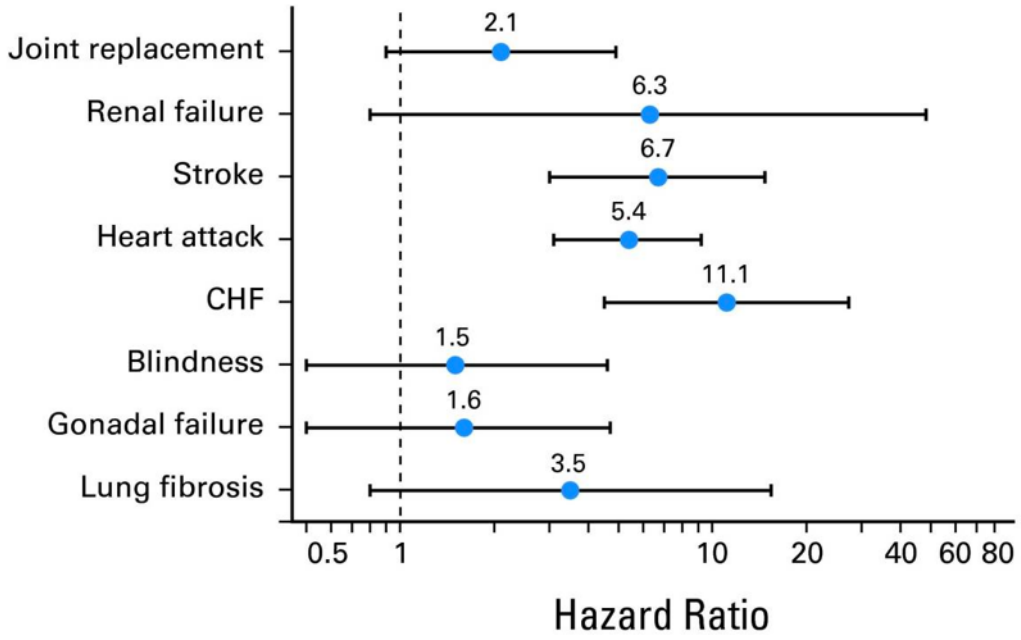
Survivor risk for chronic health conditions exceeds that of age-comparable controls



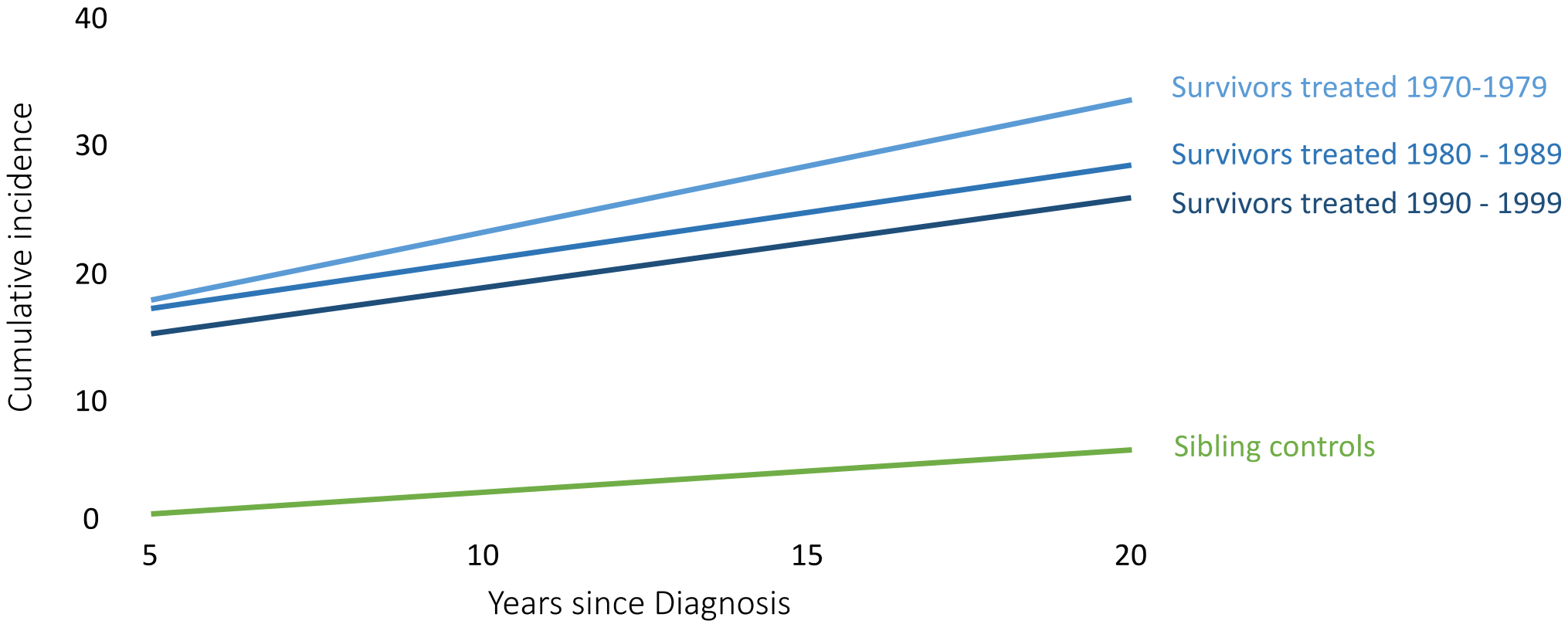
Cupit-Link et al., *ESMO Open*, 2017

Risk for new onset chronic conditions in Childhood Cancer Survivor Study participants



Armstrong et al., J of Clinical Oncology, 2014

One third of survivors develop a severe, disabling, or life threatening chronic health condition within 20 years of completing therapy



Graph modified from Gibson et al., *Lancet Oncol*, 2018

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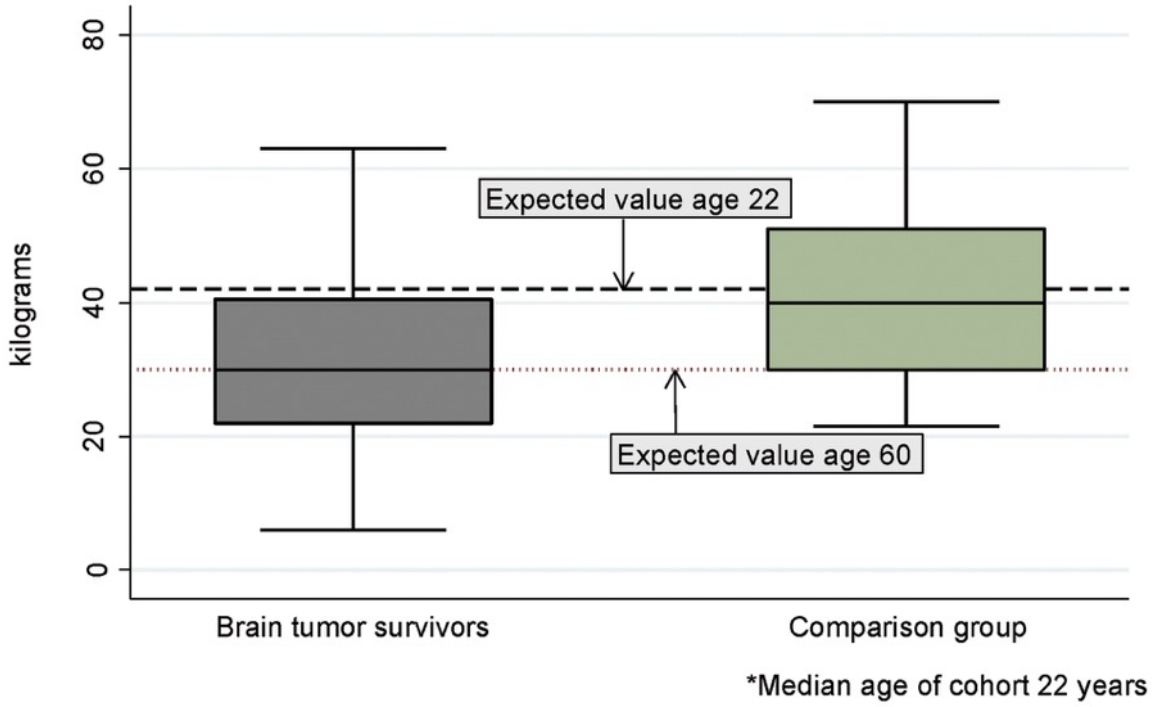
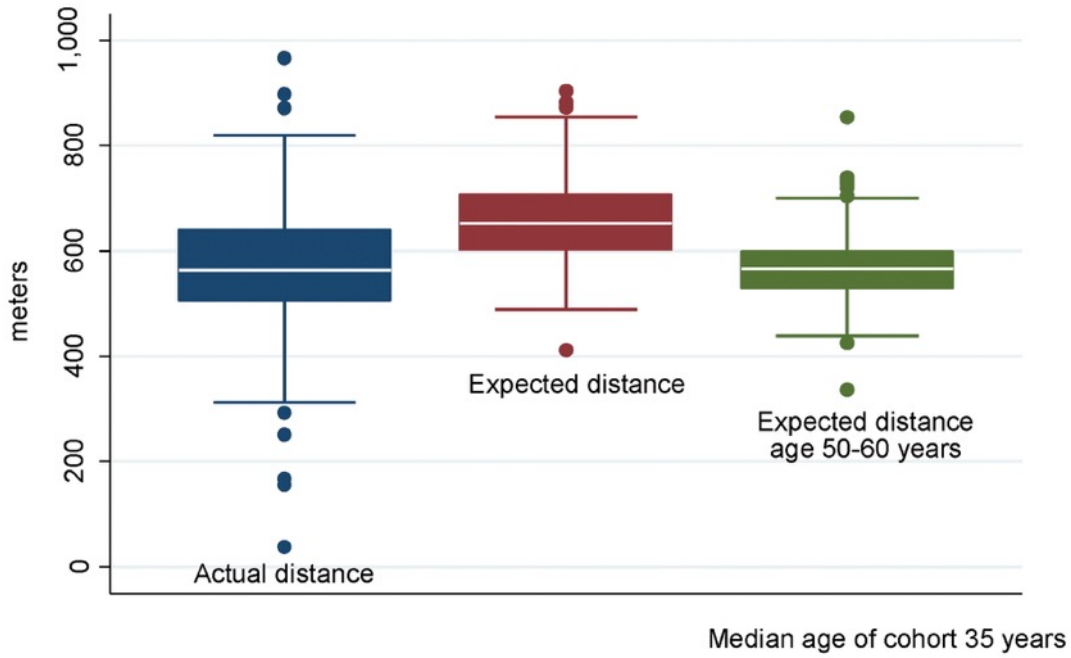
Survivors experience limitations in physical performance, such as decreased grip strength and slower walk speed, compared with age-similar controls



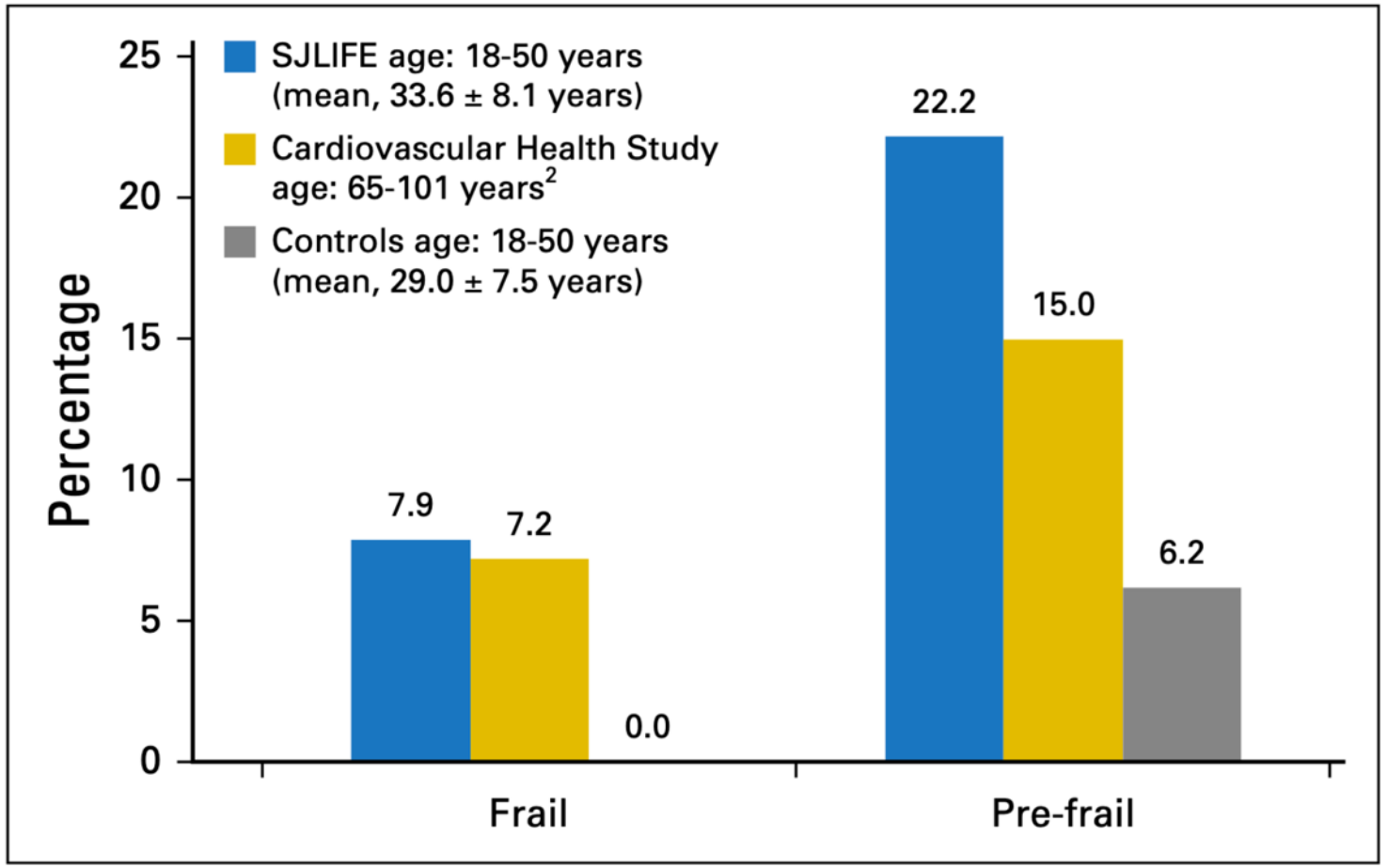
Handgrip strength, brain tumor survivors and an age- and sex-matched comparison group.



Six-minute walk distance, ALL survivors

Henderson et al., *ASCO Educational Book*, 2014

Survivors are more likely to be pre-frail and frail than age-comparable controls, approaching the frequency observed in individuals who are decades older



Ness et al., *J of Clin Oncol,* 2018

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Are the molecular mechanisms underlying physiologic aging similar to those experienced by survivors with signs of premature, accelerated aging?

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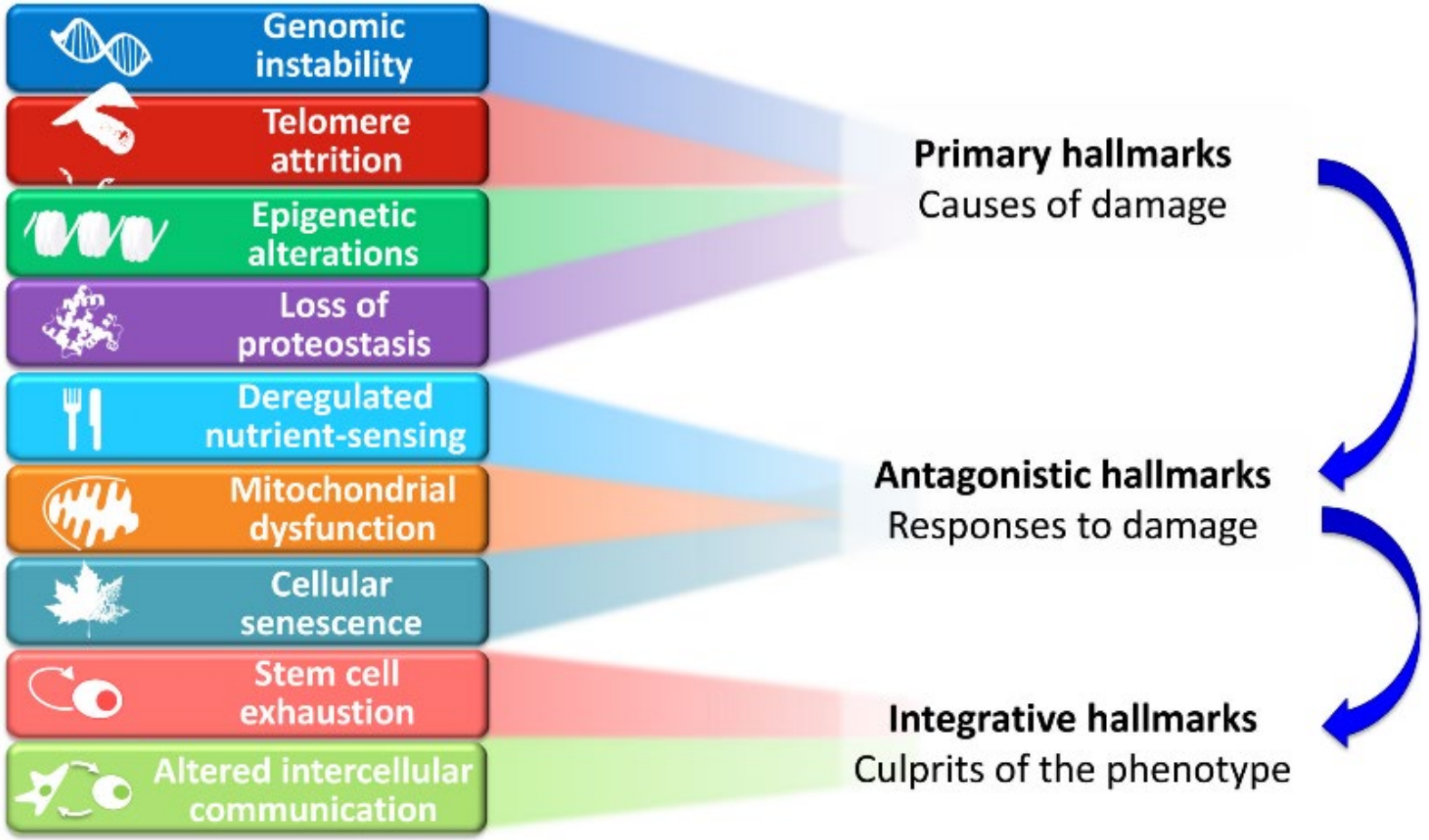
Physiologic aging is characterized by a spectrum of hallmarks associated with age-related pathology



Lopez-Otin et al., *Cell*, 2013

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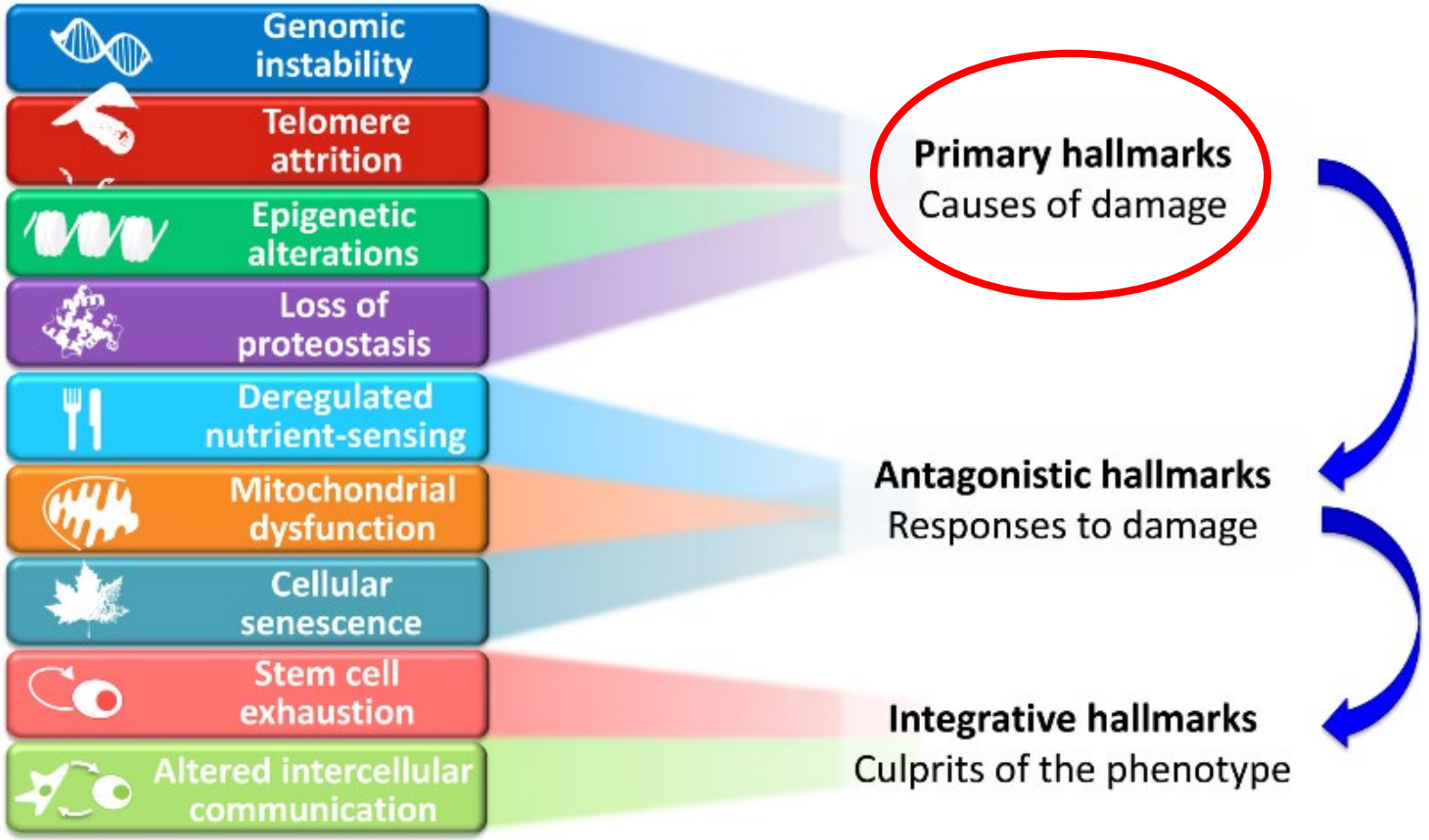

Lopez-Otin et al., *Cell*, 2013

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Primary hallmarks of physiologic aging: **Genomic instability**

- Somatic mutations, chromosomal aneuploidies, and copy number variation increase with physiologic aging
  - 10^4–10^5 DNA lesions are generated each day, arising from intrinsic (e.g. reactive oxygen species) and extrinsic sources (e.g. UV or ionizing radiation, chemotherapy)
  - Clonal hematopoiesis predicts all-cause mortality and risk of hematologic cancer
- DNA repair mechanisms resolve specific types of DNA damage (e.g. DNA mismatch repair, base-excision repair, non-homologous end joining, homologous recombination), but capacity for repair declines with increasing age
- Aging-related clinical outcomes associated with genomic instability
  - *Cancer*
  - *Neurological disease*
  - *Osteoarthritis*
  - *Mitochondrial dysfunction, cellular senescence, and stem cell exhaustion*

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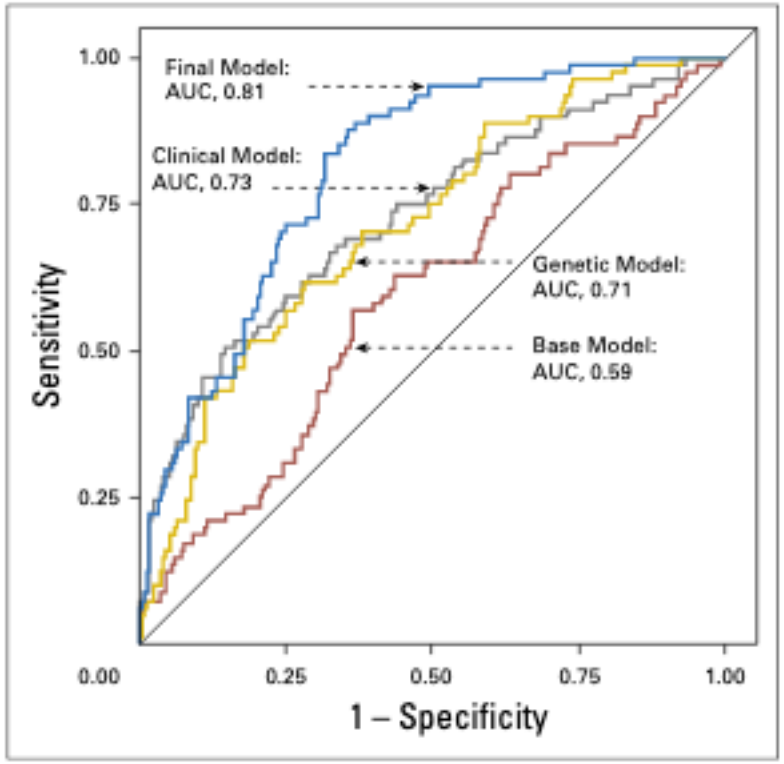
Evidence of **genomic instability** in survivors of childhood cancer

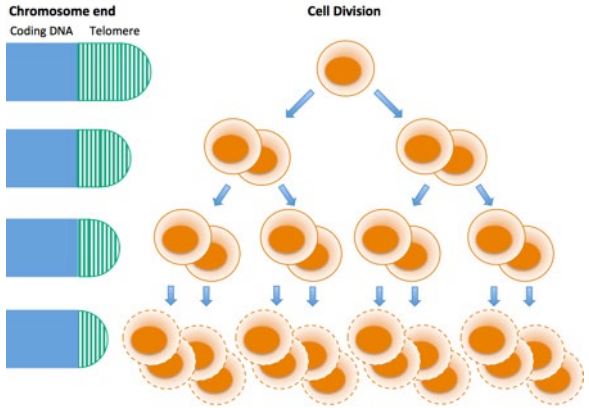
- Clinical and Genetic Risk Prediction of Subsequent CNS Tumors in Survivors of Childhood Cancer: A Report from COG ALTE03N1, *J of Clin Oncol*, 2017
- Neuroblastoma survivors are at increased risk for second malignancies: A Report from the International Neuroblastoma Risk group Project*, Eur J Cancer,* 2017
  - Variants implicating DNA repair genes associated with SMN
- *XRCC1* and glutathione-S-transferase gene polymorphisms and susceptibility to radiotherapy-related malignancies in survivors of Hodgkin disease, *Cancer*, 2004
- Repair of ionizing radiation-induced DNA damage and risk of second cancer in childhood cancer survivors, *Carcinogenesis*, 2014



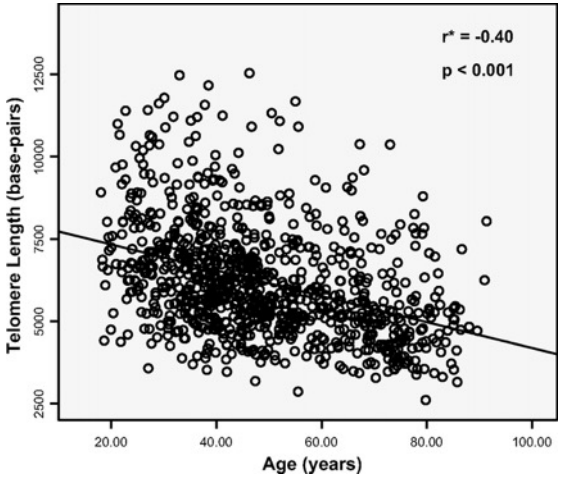
Wang et al., *J Clin Oncol,* 2017

Primary hallmarks of physiologic aging: **Telomere attrition**

- Telomeres = DNA-protein structures at chromosome ends
  - Shorten with DNA replication and with chronologic aging
  - Loss of telomeric DNA with each cell division leads to replicative senescence or apoptosis (Hayflick limit)
- Aging-related clinical outcomes associated with excess telomere attrition
  - *Cancer*
  - *Pulmonary disease*
  - *Atherosclerosis and coronary heart disease*
  - *Osteoarthritis*
  - *All-cause mortality*
  - *Poor grip strength*
  - *Sarcopenia*
  - *Cellular senescence and stem cell exhaustion*



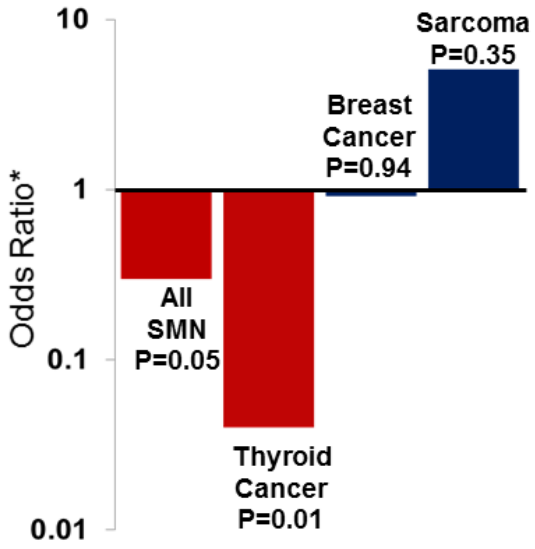
Ness et al., *JCO*, 2018



Njajou et al., *PNAS*, 2007

Evidence of **telomere attrition** in survivors of childhood cancer

- Young adult survivors of childhood acute lymphoblastic leukemia show evidence of chronic inflammation and cellular aging, *Cancer*, 2017
  - Survivors had significantly shorter TL compared with controls, especially survivors who received cranial RT
- Telomere content and risk of second malignant neoplasm in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study, *Clin Cancer Res,* 2014
- Clinical and biological markers of premature aging after autologous SCT in childhood cancer, *Bone Marrow Transplant*, 2017
  - Neuroblastoma survivors had significantly TL compared with age- and sex-matched controls



Gramatges et al., *Clin Cancer Res*, 2014

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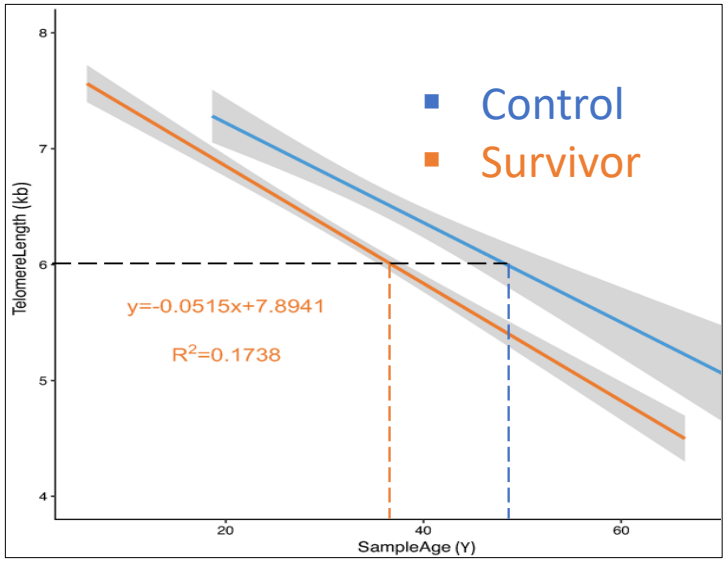
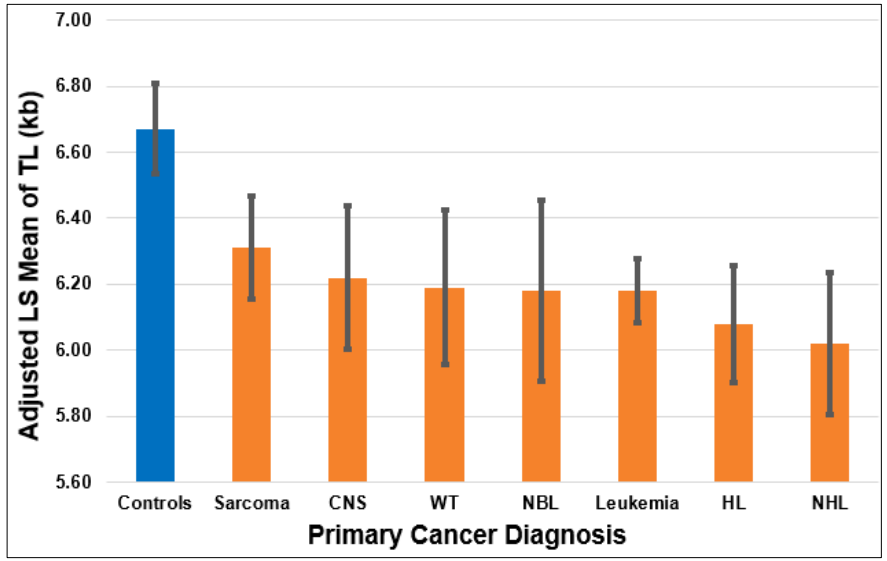
Evidence of **telomere attrition** in survivors of childhood cancer

Telomere attrition with age in the SJLIFE cohort compared with controls



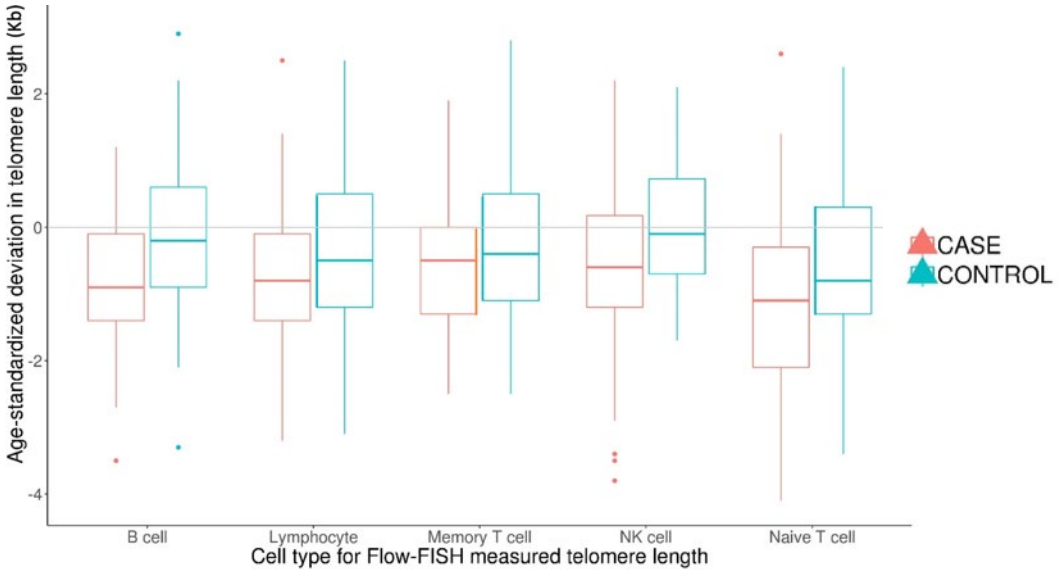
Mean LTL in SJLIFE is significantly shorter overall and across all diagnosis groups when compared to controls with no prior history of cancer



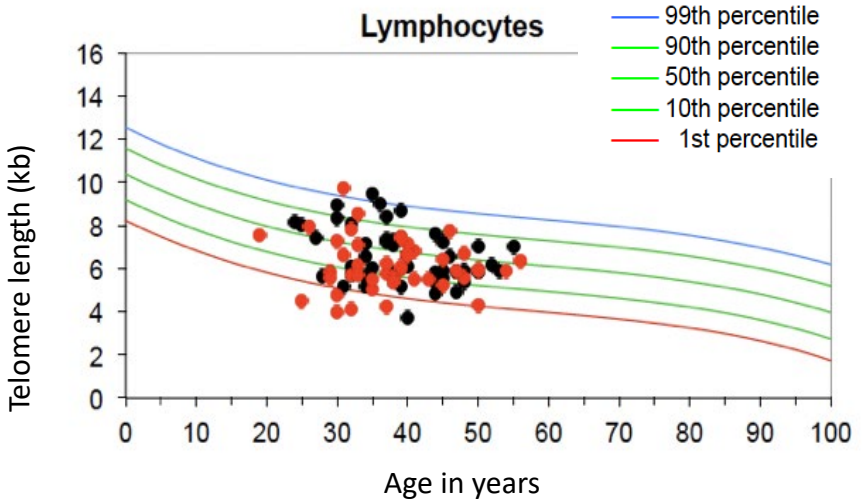
Drs. Ness, unpublished data

Evidence of **telomere attrition** in survivors of childhood cancer

Telomere shortening in leukocyte subsets among survivors enrolled to the Childhood Cancer Survivor Study with and without second cancers



LTL in CCSS survivors deviates below the population mean, with a higher than expected frequency of TL in the <1st percentile



Drs. Gramatges, unpublished data

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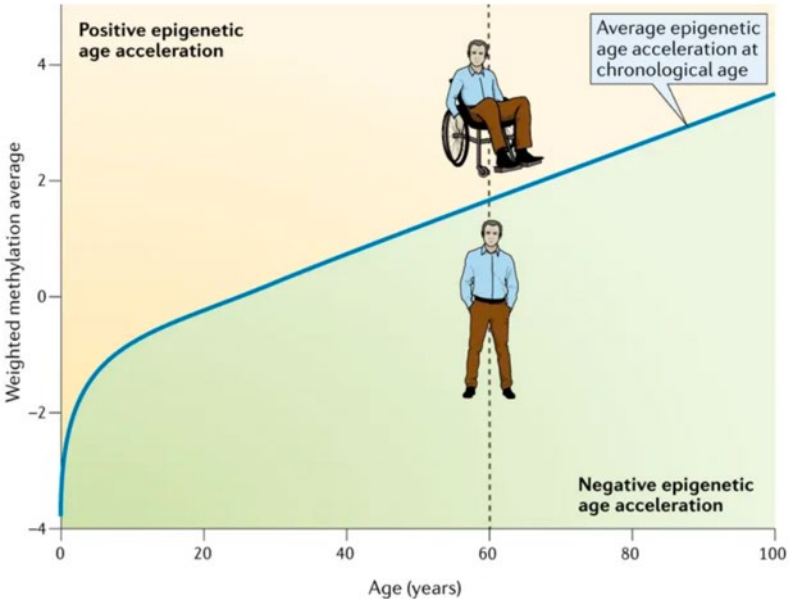
Primary hallmarks of physiologic aging: **Epigenetic alteration**

- DNA methylation (DNAm) adds methyl groups to the 5’ cytosine of C-G dinucleotides (CpGs)
- Epigenetic modification, e.g. global de-methylation and increase in site-specific variability in DNAm, occurs with aging
- Epigenetic clock: preferential hypermethylation of CpG island loci correlating with chronological age
  - **Age acceleration residual** = difference between DNAm age and chronological age
- Aging-related clinical outcomes associated with increased age acceleration residuals
  - *Frailty*
  - *Poor grip strength, sarcopenia*
  - *Cancer*
  - *Type II diabetes, neurological disease*



Horvath et al., *Nat Rev Genet,* 2018

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Evidence of **epigenetic alteration** in survivors of childhood cancer

- DNA methylation patterns of adult survivors of adolescent/young adult Hodgkin lymphoma compared to their unaffected monozygotic twin, *Leuk Lymphoma*, 2019
  - Excess epigenetic aging (blood DNAm age) in survivors
- DNA methylation and obesity in survivors of pediatric acute lymphoblastic leukemia: A report from the Childhood Cancer Survivor Study, *Genes Chromosomes Cancer*, 2019
  - BMI-DNAm loci associated with obesity in ALL survivors treated without CRT
- T cell epigenetic remodeling and accelerated epigenetic aging are linked to long-term immune alterations in childhood cancer survivors, *Clin Epigenetics*, 2018
  - Accelerated epigenetic aging in T cells associated with chronic inflammatory disease in survivors
- DNA methylation of a novel PAK4 locus influences ototoxicity susceptibility following cisplatin and radiation therapy for pediatric embryonal tumors, *Neuro Oncology*, 2017
  - A CpG methylation loci (cg14010619) is associated with ototoxicity severity

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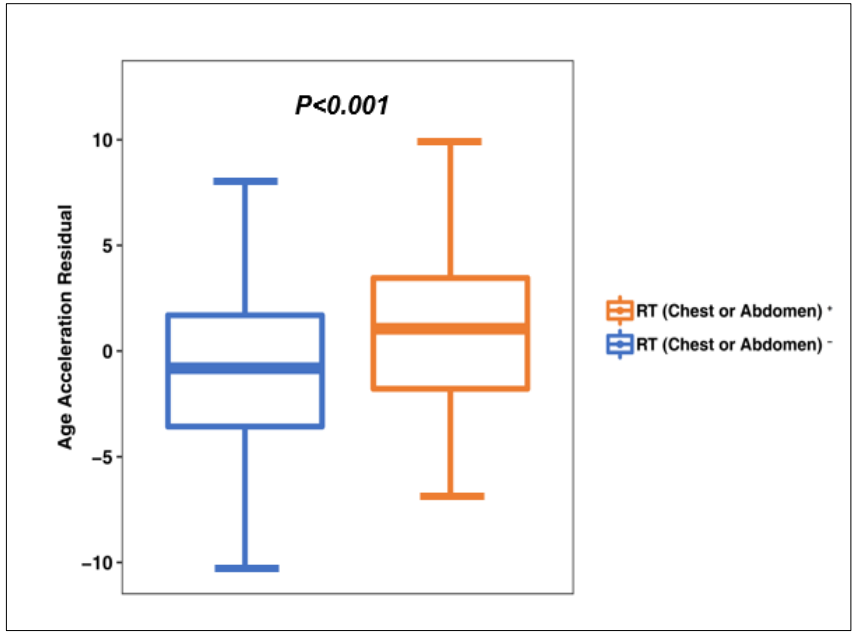
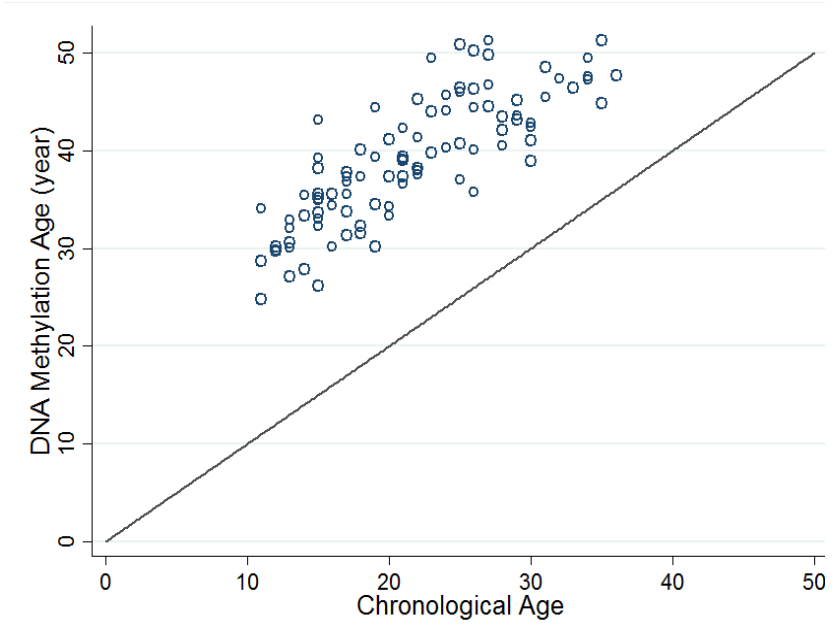
Evidence of **epigenetic alteration** in survivors of childhood cancer

In the SJLIFE cohort, the age acceleration residual was increased among survivors exposed to chest or abdominal RT vs. survivors not exposed to RT, suggesting RT contributes to accelerated epigenetic aging. The age acceleration residual was also associated with TL (adjusted model), explaining 4% of variance in TL**.**



In CCSS, ALL survivors (n=96) DNAm age exceeds chronologic age by **17.8 years** (p <0.0001). Age at diagnosis was inversely correlated with age acceleration residual (p=0.001), suggesting younger subjects are more susceptible to accelerated epigenetic aging.



Drs. Ness, Lupo, and Gramatges, unpublished data

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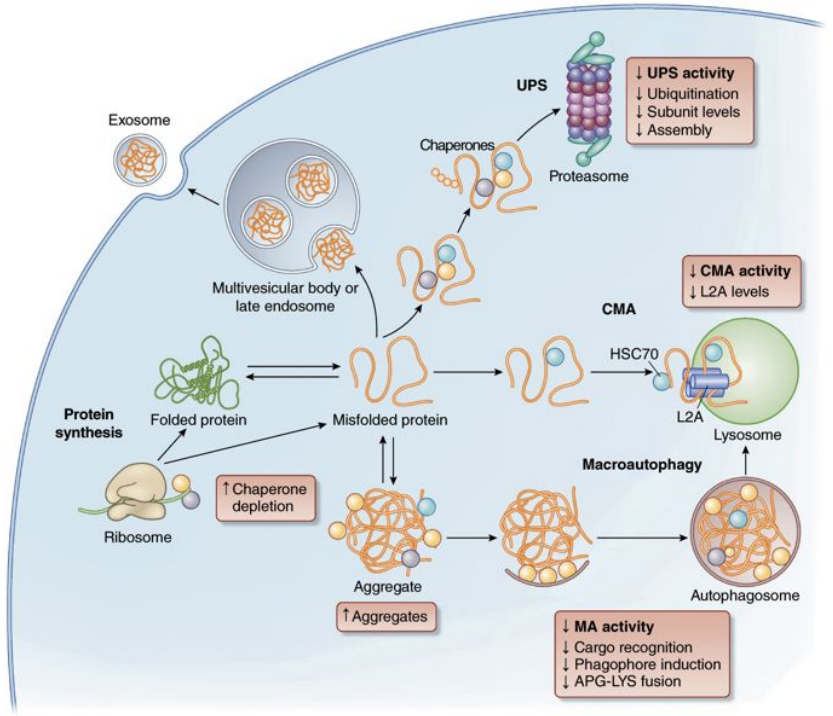
Primary hallmarks of physiologic aging: **Loss of proteostasis**

- Proteolytic pathways responsible for unfolded protein quality control become hypofunctional with aging
  - Autophagy–lysosomal system
  - Ubiquitin-proteasome system
- Aging-related clinical outcomes associated with impaired/dysregulated proteostasis
  - *Alzheimer's disease*
  - *Parkinson's disease*
  - *Cataracts*
  - *Pulmonary disease*



Kaushik et al., *Nat Med*, 2015

Other correlative biological/molecular evidence of aging-related pathology in survivors of childhood cancer: **Inflammation**

- Young adult survivors of childhood acute lymphoblastic leukemia show evidence of chronic inflammation and cellular aging, *Cancer*, 2017
  - Plasma levels of IL-2, IL-10, IL-17A, and CRP significantly higher vs. healthy controls
- Clinical and biological markers of premature aging after autologous SCT in childhood cancer, *Bone Marrow Transplant*, 2017
  - Higher levels of CRP among survivors than controls
- Impact of sleep, fatigue, and systemic inflammation on neurocognitive and behavioral outcomes in long-term survivors of childhood acute lymphoblastic leukemia, *Cancer*, 2017
  - Worse executive function, processing speed, and behavioral symptoms in female survivors with higher levels of IL-6, IL-1β, and CRP
- Elevated markers of inflammation and endothelial activation and increased monocyte counts in adult survivors of childhood ALL, *Immunobiology*, 2013
  - Chronic inflammatory activation and immune dysregulation in adult survivors

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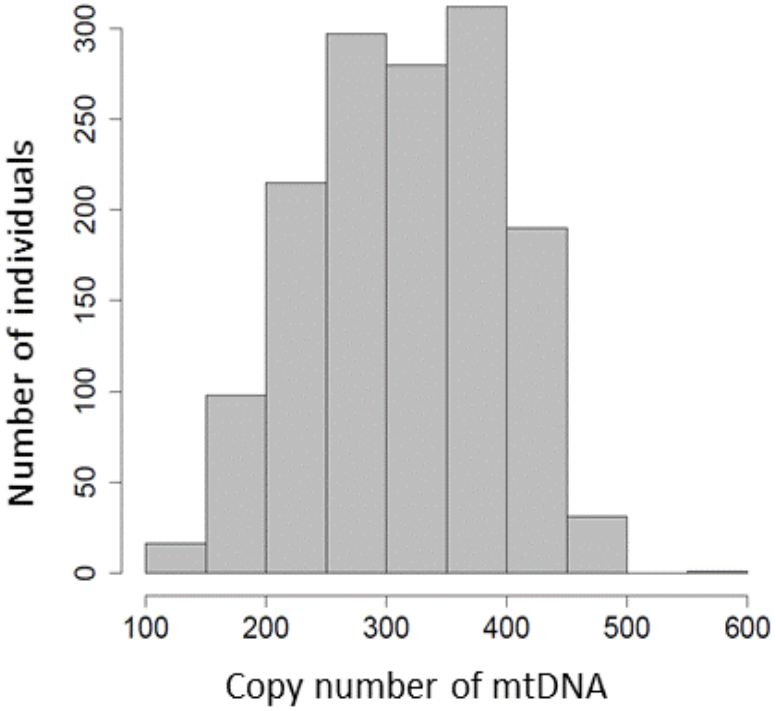
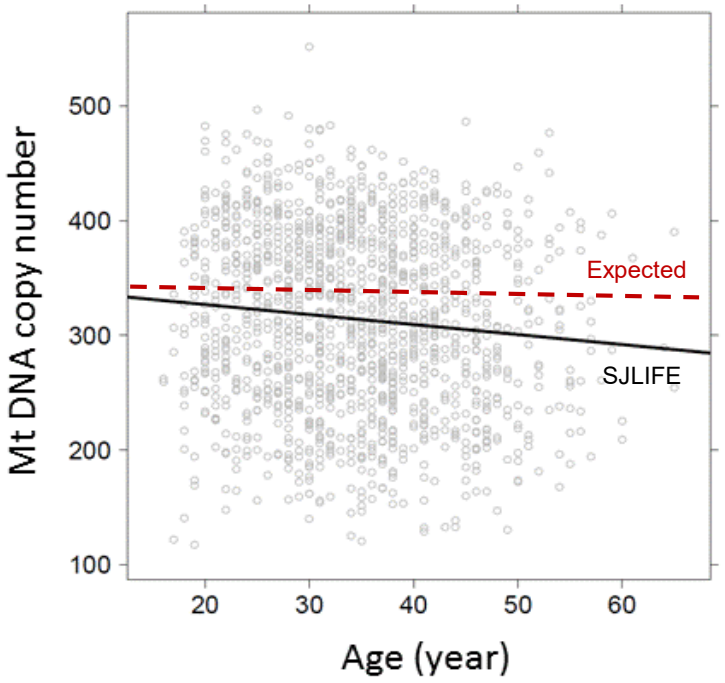
Other correlative biological/molecular evidence of aging-related pathology in survivors of childhood cancer – **oxidative stress and mitochondrial dysfunction**

- Polymorphisms in Genes Related to Oxidative Stress Are Associated With Inferior Cognitive Function After Therapy for Childhood Acute Lymphoblastic Leukemia, *J Clin Oncol,* 2015
  - Inferior cognitive or behavioral outcomes associated with SNPs in genes related to oxidative stress and/or neuroinflammation
- Accelerated atherosclerosis, hyperlipoproteinemia and insulin resistance in long-term survivors of Hodgkin lymphoma during childhood and adolescence, *Neoplasma*, 2019
  - Markers of oxidative stress (oxidation protein products, oxidized low-density lipoprotein), inflammation (CRP) and endothelial dysfunction (E-selectin, PAI-1) higher in HL survivors

Other correlative biological/molecular evidence of aging-related pathology in survivors of childhood cancer –**mitochondrial dysfunction**

In the SJLIFE cohort, mitochondrial copy number declines with age at a faster rate than expected among childhood cancer survivors, with a loss of 9 copies per ten years compared to an expected loss of 1.5 copies per 10 years.





Drs. Ness, unpublished data

Other correlative biological/molecular evidence of aging-related pathology in survivors of childhood cancer: **Cellular senescence**

- Muscle weakness, frailty, metabolic and cardiovascular dysfunction, risk for second cancers, and pulmonary fibrosis, conditions common to survivors, have been associated with cellular senescence in non-survivor populations
- Expression of the senescence marker p16INK4a in skin biopsies of acute lymphoblastic leukemia survivors: a pilot study, *Radiat Oncol*, 2013
  - p16INK4a mRNA levels were 5.8 times higher in scalp skin biopsies (targeted by cranial RT) compared to buttocks skin biopsies

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Potential interventions targeting mechanisms of aging

Intervention	Effects
Deubiquitylase inhibitors and proteasome activators	Clearance of harmful protein in human cells
Metformin	Activation of telomerase expression, reduction of reactive oxygen species, decreased IGF signaling
Exercise	Reduce chronic inflammation, mitigate age-related telomere attrition, alteration of DNA methylation patterns
Caloric restriction/intermittent fasting	Decreased IGF signaling, mTOR inhibition, sirtuin activation, autophagy activation
Resveratrol and polyphenols	Upregulation of SIRT1 activity, promotion of autophagy
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
Danazol	Telomere maintenance/lengthening

Conclusions…

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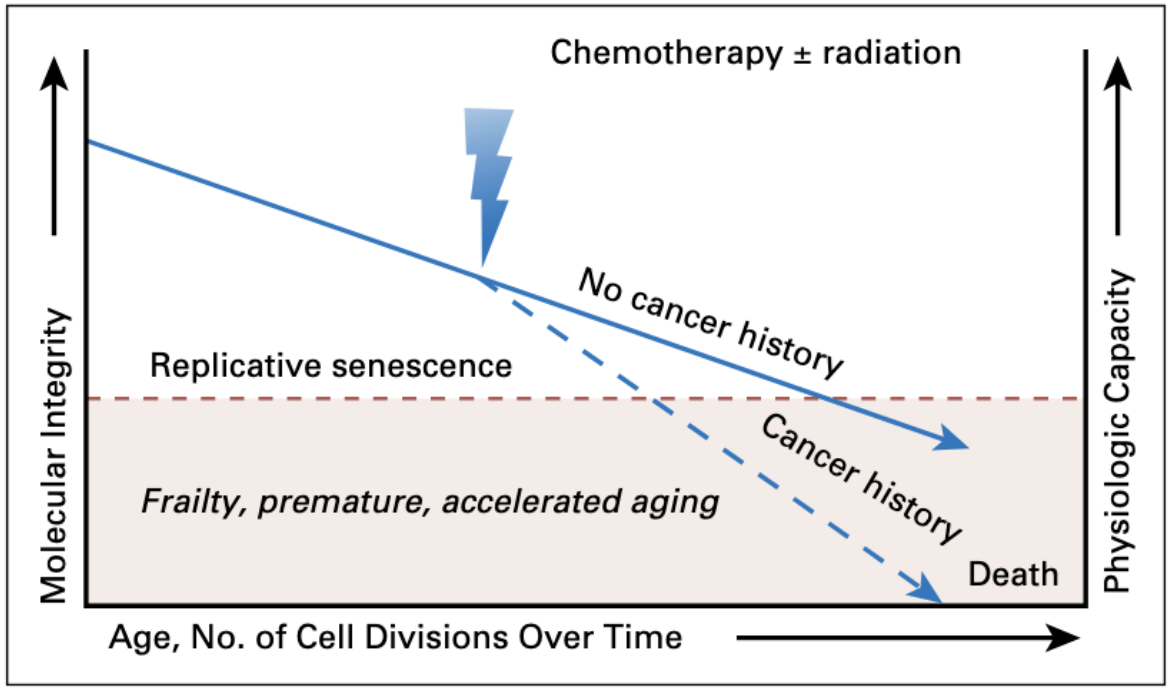
Insults to molecular integrity and physiologic capacity provoked by exposure to chemotherapy and/or radiation may be associated with an excess risk and advanced onset of age-related diseases and frailty in survivors of childhood cancer



Ness et al., *J of Clin Oncol,* 2018

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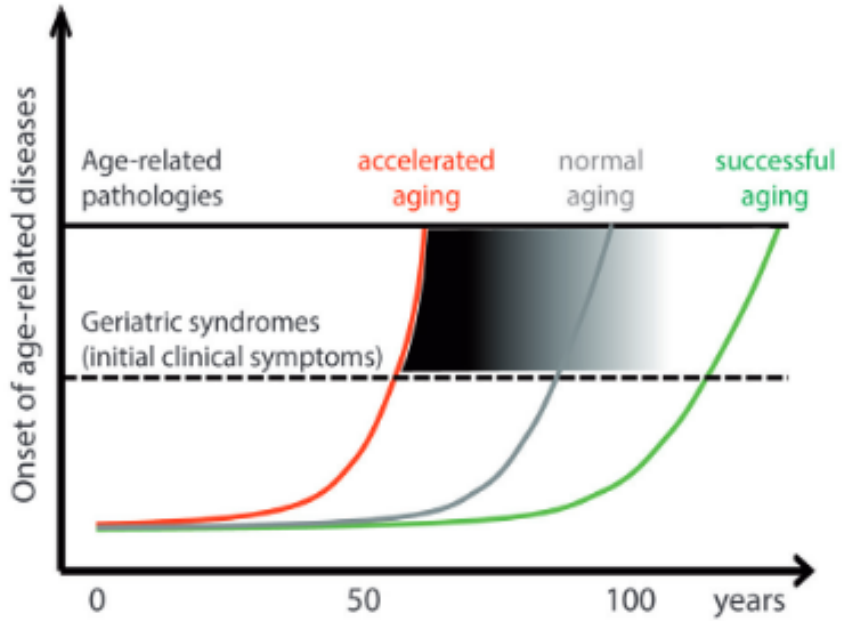
Physiologic aging is a complex, multifactorial process influenced by genetic, epigenetic, and environmental factors



Franceschi et al., *Frontiers in Medicine*, 2018

The phenotypic differences between physiologic aging and the early aging experienced by survivors are not yet clear, nor are distinctions in the molecular mechanisms that drive these phenotypes

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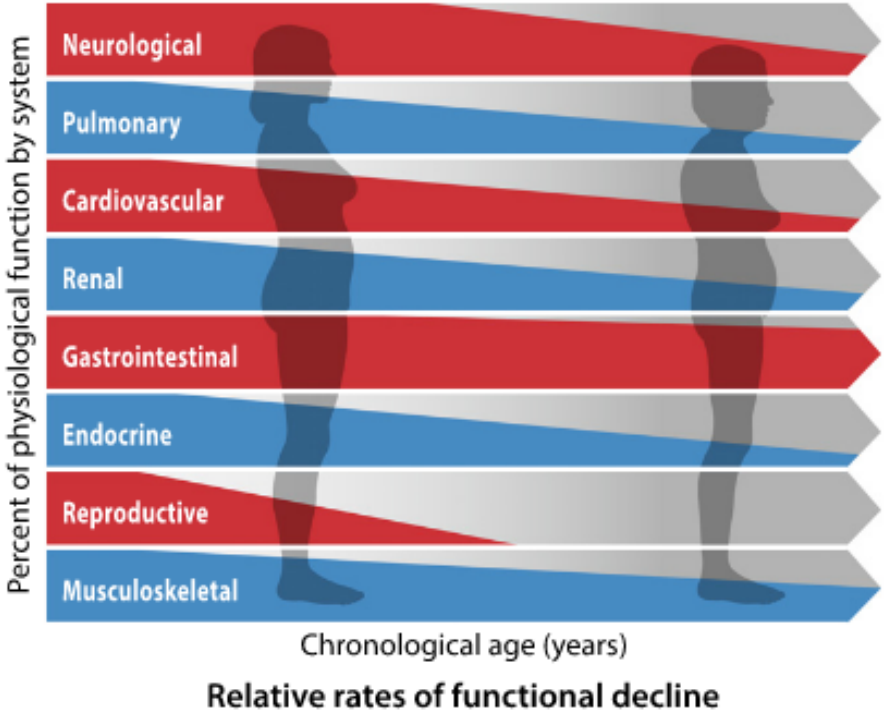
Physiologic aging is characterized by disparities in functional decline between organ systems, suggestive of inherent variation in tissue susceptibility to chronologic aging



Among survivors, chemotherapy and radiation may differentially impact specific organ systems, leading to organ-specific accelerated aging that is dependent on the cumulative effect of treatment exposures

Khan et al., *Aging Cell*, 2017

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Final thoughts regarding grant development: *considerations and lessons learned*

- Rigor of prior research
  - Is there evidence for association with aging-related outcomes in cancer survivor populations?
  - Preliminary data?
- Consider molecular mechanisms associated with organ-specific outcomes
  - e.g. markers of oxidative stress in studies investigating cardiotoxicity in survivors
- Provide rationale for limiting investigation to a subset of biomarkers
- Acknowledge and anticipate potential differences between physiologic aging and survivor aging, for both the phenotype and the underlying molecular mechanisms
- Consider the relationship of the outcome with longitudinal changes in biomarkers over time, if possible
- Cost, feasibility, power

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Q&A

Future webinars

April 9, 2020, 12-1 p.m. ET

- Luigi Ferrucci and Morgan Levine

Send speaker suggestions and other feedback to:

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