Premature Aging and Frailty in Cancer Survivors

September 9, 2022
Kirsten K. Ness, PT, PhD, FAPTA
Overview

• Characterizing accelerated aging/frailty in survivors
  – Disease and deficit accumulation
  – Phenotypic frailty
  – Biologic markers of aging
• Interventions to remediate frailty by target(s)
  – Specific disease and deficit targets
  – Phenotypic targets
  – Biologic targets
• Interventions to prevent frailty in young survivors and current patients
Characterizing Frailty

<table>
<thead>
<tr>
<th>Deficit Accumulation</th>
<th>Phenotypic</th>
<th>Biologic markers of aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frailty as an accumulation of chronic diseases, difficulty with activities of daily living, emotional health, cognition, sleep quality, others</td>
<td>Pre-defined measures of poor physiologic health</td>
<td>Molecular evidence of cellular aging</td>
</tr>
<tr>
<td>No specified set of criteria – count of total (30-40 are typical)</td>
<td>Specified criteria</td>
<td>Postulated to include singular or multiple measures of telomere attrition, genomic instability, epigenetic alterations, loss of proteostasis, dysregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication</td>
</tr>
<tr>
<td></td>
<td>• Muscle wasting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Muscle weakness</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Slow walking speed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low energy expenditure</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frail ≥ 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-frail = 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not frail &lt; 2</td>
<td></td>
</tr>
</tbody>
</table>
Childhood Cancer Survivor Study (CCSS)

- Multi-institutional cohort
  - 31 institutions w/ n=25,665 survivors
- Funded in 1994
- Retrospective cohort
- Diagnosed 1970-1999
- 5-year survival
- Leukemia, lymphoma, CNS, bone, Wilms tumors, neuroblastoma, soft-tissue and bone sarcoma
- Detailed treatment data
- Wide range of outcomes
Chronic Disease in the CCSS Cohort

- Chronic disease categorized among 23,601 survivors and 5,051 siblings using Common Terminology for Adverse Events (CTCAE v 4.03)

- 20-year cumulative incidence by decade of diagnosis
  - 33.2% (95%CI 32.0-34.3%) 1970-1979
  - 29.3% (95%CI 28.2-30.2%) 1980-1989
  - 27.5% (95%CI 26.4-28.6%) 1990-1999
  - 4.6% (95%CI 3.9-5.3%) Siblings

- Changes in chronic disease incidence among survivors consistent with changes in treatment over time

Gibson 2018 Lancet Oncol

Cumulative incidence of a first grade 3–5 condition

Enrollment of On-Campus Participants in SJLIFE (March 2020)

- Enrollment
  - 6,005 survivors
  - 773 controls
- Completed ≥ 1 evaluation
  - 5,223 survivors
  - 736 controls
- Participation
  - 80.3% overall participation
  - > 90% among those contacted

Howell 2020 Int J Epidemiol
## SJLIFE Cohort Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall Cohort (5+ Year Survivors diagnosed 1962-2012)</th>
<th>Recruitment for Clinical Assessment</th>
<th>Survivors</th>
<th>Frequency Matched Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Eligible</td>
<td>Enrolled</td>
</tr>
<tr>
<td><strong>Survival Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>87.5%</td>
<td>100%</td>
<td>5753</td>
<td>629</td>
</tr>
<tr>
<td>Dead</td>
<td>12.5%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>45.3%</td>
<td>46.0%</td>
<td>54.0%</td>
<td>52.1%</td>
</tr>
<tr>
<td>Male</td>
<td>54.7%</td>
<td>54.0%</td>
<td>46.0%</td>
<td>47.9%</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>79.3%</td>
<td>79.1%</td>
<td>52.1%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Black</td>
<td>16.9%</td>
<td>17.0%</td>
<td>16.4%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Other</td>
<td>3.6%</td>
<td>3.7%</td>
<td>3.1%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.1%</td>
<td>1.0%</td>
</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.1%</td>
<td>95.7%</td>
<td>96.2%</td>
<td>96.0%</td>
</tr>
<tr>
<td>No</td>
<td>95.9%</td>
<td>4.3%</td>
<td>3.8%</td>
<td>4.0%</td>
</tr>
</tbody>
</table>

*Howell 2020 Int J Epidemiol*
Cumulative Burden of Chronic Disease in SJLIFE

- 5522 survivors (≥ 10 years from primary diagnosis and ≥ 18 years of age at assessment)
- 272 community controls
- 168 chronic conditions graded using a modified version of the Common-Terminology for Adverse Events (CTCAE) v4.03
- By age 50 years, average number of grade 3-5 chronic conditions among survivors was 4.7 (95% CI 4.6-4.9), 2-fold higher than community controls

*Bhakta 2017 Lancet, Hudson 2017 Cancer Epidemiol Biomarkers Prev*
Changing Distribution of Chronic Disease Type by Treatment Era

980 ALL survivors
- ≥ 10 years from primary diagnosis
- 50% female
- ≥ 18 years at assessment (median 35.8, IQR 9.4-42.9)
- Median age at diagnosis 5 years (IQR 3.1-9.1)
- Median time from diagnosis 30.0 years (IQR 22.7-36.3)

111 conditions grouped by organ system

Age standardized to 30 years old

Mulrooney 2019 Lancet Haematol
Physiologic Aging – Phenotypic Frailty

- Loss of physiological capacity that interferes with normal function
- 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; predictor of early mortality

Adapted from Buchner 1992 Clin Geriatr Med
Physiologic Aging – Phenotypic Frailty

Adapted from Buchner 1992 Clin Geriatr Med

Disease
Chemotherapy
Radiation
Surgeries

Physiologic Capacity

NOT FRAIL

FRAIL

DEATH

Physiologic Aging – Phenotypic Frailty

Adapted from Buchner 1992 Clin Geriatr Med

Physiologic Capacity

Disease
Chemotherapy
Radiation
Surgeries

NOT FRAIL

Tailored interventions

FRAIL

DEATH

Age →
Physiologic Aging – Phenotypic Frailty

- Disease
- Chemotherapy
- Radiation
- Surgeries

Tailored interventions

Adapted from Buchner 1992 Clin Geriatr Med
Physiologic Aging – Phenotypic Frailty

Five components of fitness:
- Muscle wasting
- Muscle weakness
- Self-reported exhaustion
- Slow walking speed
- Low energy expenditure

Frail: ≥ 3 components
Pre-frail: 2 components
Frailty in 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 cranial radiation exposure

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>N</th>
<th>Deaths</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frailty</td>
<td>151</td>
<td>4.6%</td>
<td>2.6 (1.5-2.8)</td>
</tr>
<tr>
<td>No Frailty</td>
<td>1771</td>
<td>1.4%</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for age and number of chronic medical conditions CTCAE v4.03 grade ≥ 3

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

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>SJLIFE age 18-50 years (mean 33.6 ± 8.1)</th>
<th>Cardiovascular Health Study age 65-101 years</th>
<th>Controls age 18-50 years (mean 29.0 ± 7.5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frail</td>
<td>7.9</td>
<td>7.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Pre-frail</td>
<td>22.2</td>
<td>15.0</td>
<td>6.2</td>
</tr>
</tbody>
</table>

Ness 2018 J Clin Oncol
Component | Definition (≥ 3 of following)
---|---
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

10,899 members of the Childhood Cancer Survivor Study (CCSS) ≥ age 18 years and alive at the end of follow-up

**Validation of the Frailty Phenotype in CCSS**

**Hayek 2020 J Clin Oncol**

**Finding cures. Saving children.**
Progression of Frailty in SJLIFE

- 1,509 survivors invited for a second visit five years after their baseline visit
- ≥ 10 years from diagnosis
- 18 - 45 years of age (median 30) at baseline from 2008 - 2013
- 51.6% male
- 16.1% non-white
- 37.9% leukemia/19.5% lymphoma/10.9% CNS tumor/31.7% solid tumor

There were 77 deaths in the cohort, 17.4% among those who were frail and 4.3% among those who were not frail at baseline (HR 3.53, 95% CI 1.95-6.38 after accounting for chronic conditions).

Delaney 2021 J Natl Cancer Inst
Prevalence of Frailty by Component

Baseline
Follow-up

Low lean mass: 18.5% (Baseline), 23.3% (Follow-up)
Slow walking speed: 1.5% (Baseline), 6.9% (Follow-up)
Muscle weakness: 10.9% (Baseline), 17.9% (Follow-up)
Low energy expenditure: 37.0% (Baseline), 53.7% (Follow-up)
Exhaustion: 23.8% (Baseline), 28.2% (Follow-up)

all p < 0.001*
Hallmarks of Aging and Interconnections

Lopez-Otin 2013 Cell
Leukocyte Telomere Length (LTL) and Epigenin Survivors and Controls

Age-dependent LTL Attrition

Epigenetic Age Acceleration

Song 2020 Clin Cancer Res

Qin 2020 J Natl Cancer Inst
**Sarcopenia and Mitochondrial Copy Number in Survivors**

- Sarcopenia defined as appendicular lean muscle mass (by DEXA), +/- hand grip strength ≤ -1.5 SDS age, sex and race specific values in 1,824 survivors (45% 18-24 years of age, 55% ≥ 25 years of age).
- 11.7% had low lean mass and 4.8% had both low lean mass and hand grip weakness.
- Mitochondrial DNA copy number (mtDNAcn) was estimated from whole genome sequencing and validated with qPCR in a subset of the sample.

Mean mtDNA copy number is 314.3±77.8. Mean rate of decrease is 9/10 year (compared to 1.5/10 year in general population)

A one standard deviation lower mtDNA copy number is associated with a 1.28 (95% CI 1.11-1.47) increased odds of low lean mass and a 1.42 (95% CI 1.14-1.78) increased odds of both low lean mass and hand grip weakness.
• 59 survivors of childhood cancer exposed to chemotherapy.
• p16\(^{INK4a}\) mRNA expression in peripheral blood T-lymphocytes was associated with walking speed and abnormal body composition.

Goodenough 2022 Unpublished Data

Interventions to RemEDIATE Frailty in Survivors

• Targeting Accumulated or Specific Deficits (and some markers of aging)
  – Prediabetes
  – Cardiopulmonary Fitness

• Targeting Phenotypic Frailty
  – Protein Supplementation and Resistance Training

• Targeting Molecular Aging
  – Senolytics
A Pilot Intervention Trial for Diabetes Prevention Among Prediabetic, Adult Survivors of Childhood Cancer

To establish the feasibility and safety of a combined metformin + app-based lifestyle intervention among adult survivors with prediabetes and assess preliminary evidence for efficacy of the combined metformin + app-based lifestyle intervention.

Work supported by The St. Baldrick’s Foundation and Conquer Cancer, The ASCO Foundation
Components of Lifestyle Intervention

Core-curriculum, daily content

Most of your diet won’t be green foods – and that’s fine.

It’s important to remember that “red” doesn’t mean bad and “green” doesn’t mean good. We like to think of our color system as a portion guide and recommend the following breakdown:

- Green: 30%
- Yellow: 45%
- Red: 25%

“Red” foods simply raise a “red flag” for foods that contain a lot of calories without filling you up! So while you can eat “green” foods in larger quantities, you need to be more mindful of how much “red” foods you’re eating.

Food logging with feedback

Customizable “SOS” to stay on track

Test the efficacy of a telehealth-based interventions (individually-tailored aerobic and strength) to improve functional capacity as assessed by measures of exercise capacity, cardiac, pulmonary, musculoskeletal and neurosensory function.

We will also measure changes in methylation profiles from baseline to week 20.

U01 CA246570 (Ness, Jefferies)
Remote-Home Based Delivery
Remote-Home Based Delivery

Survivor 18 to 39 years of age with low lean mass

Resistance training and placebo

Resistance training and supplement

57 completed the 24-wk intervention at local gym
- 24 in RT + S
- 33 in RT + P

Adherence
- RT + S group completed 74.8% of sessions
- RT + P group completed 67.0% of sessions

Mean age 33.1 ± 7.0 years
67% white, 47% female

To evaluate the effects of 24 weeks of supervised resistance training with or without protein supplementation (21 gm of whey protein/day) on muscle mass and strength.

Krull M 2020 Med Sci Sports Exerc
Protein Supplementation & Resistance Training

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg press</td>
<td>185</td>
<td>190</td>
</tr>
<tr>
<td>Knee extension</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>Chest press</td>
<td>65</td>
<td>60</td>
</tr>
<tr>
<td>Tricep curls</td>
<td>25</td>
<td>22</td>
</tr>
</tbody>
</table>
Test the efficacy of senolytic agents (combination of Dasatinib plus Quercetin, and Fisetin alone) to improve frailty measures, senescent cell abundance in blood, markers of inflammation, insulin resistance, bone resorption and cognitive function.

U01 CA246510 (Armstrong)
Interventions to Prevent Frailty

• Soon after Treatment
  – Rewards Based Physical Activity
  – Parent Centered Health Intervention

• During Treatment
  – Aerobic Training
  – Exercise and NAD+
Rewards- and Web-based Physical Activity Intervention for Children with Cancer (ALTE1631)

**Primary Aim**
- Does social interaction and rewards help improve fitness (PCI)?

**Study Design**
- 18 months long, 4 clinic visits every 6 months
- Intervention period first 6 months
- 2 Groups
  - **Control**: See their own activity; earn rewards (received after intervention period)
  - **Intervention**: See their own and others activity; interact with others; earn rewards (received during intervention period)

**Eligibility**
- 8-15 years old
- All cancer cases with ICD-O code of 2 or 3, in remission
- Completed therapy in past **12 months**
- Not too active
- Physically able to participate
- No impairments that prevent computer use
Platform/Device

engage MovBand 5

MOV BAND 5
Fitness Tracker

Moves on the App

**App Features - Home Screen**

- Steps
- Kilometers
- Moves
- Calories
- Heart Rate
- Sleep Data
- Challenge
- Sport Record
- Alarm
- Sedentary Reminder
‘Move’ Website Dashboard - Activity

- My Progress
  - Total Moves
  - Avg Daily Moves
  - Goal Daily Moves
  - % Towards Goal
  - Last Sync
Challenges for the Intervention Group

**App Features - Home Screen**

- Steps/Km/Moves/Calories
- Heart Rate
- Sleep Data

**Challenge**
- Date Range
- Goal
- Rank
- Daily Avg Steps
- Leaderboard

- Sport Record
- Alarm
- Sedentary Reminder
Challenges for the Intervention Group

- ‘Move’ Dashboard - Challenges
  - Your Challenges
    - My Stats
    - Goal
    - Avg Daily Moves
    - Your Rank
    - Days Remaining
  - My Leaderboards
• Targeting parents/caregivers as change agents to modify home environmental factors to improve young ALL survivor (4-12 y) sleep habits, physical activity, screen time, dietary behaviors

• Aims:
  – To evaluate the efficacy of a parent-targeted, telehealth-delivered intervention, the Healthy Kids after Cancer program, on children’s health behavior.
  – To determine the impact of the intervention on children’s BMI trajectories, cardiometabolic health, and neurobehavioral (i.e., neurocognitive and emotional-behavioral) functioning.
  – To examine factors influencing intervention adherence and implementation.
Aim 1: Intervention Impact on Children’s Health Behaviors
- Actigraphy Measured Sleep and Physical Activity
- Gold Standard Dietary Recalls
- Screen Time Survey

Aim 2: Intervention Effect on Children’s Cardiometabolic Health and Neurobehavioral Function
- Anthropometric/Body Composition
- Metabolic Parameters
- Inflammation/Oxidative Stress
- NIH Toolbox Neurocognitive Performance
- Survey of Emotions and Behavior

Aim 3: Factors Influencing Intervention Implementation
- Patient Factors: Medical Record Review (e.g., neuropathy, age, ethnicity, neurotoxicity)
- Caregiver Factors: Demographics, Caregiver Survey (e.g., stress, child vulnerability)
- Healthcare Provider Factors: Administrative Data (e.g., provider type)

Survivor Education Control
- 6-month Follow-up (Post-Intervention)
- 12-month Follow-up

Healthy Kids After Cancer Intervention
- Baseline Assessment
- Consent Procedures
- Identified Eligible Families
- Randomization
- Actigraphy Measured Sleep and Physical Activity
- Gold Standard Dietary Recalls
- Screen Time Survey

Randomization
- Baseline Assessment
- Consent Procedures
- Identified Eligible Families

Healthy Kids After Cancer Intervention
- Baseline Assessment
- Consent Procedures
- Identified Eligible Families
- Randomization
# Healthy Kids After Cancer: Intervention

**Table 1. Healthy Kids after Cancer Session Topics**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Common Cancer-Related Challenges</th>
<th>Week</th>
<th>Topics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary Intake</td>
<td>During treatment it was natural for parents to allow the child to eat or drink anything, healthy or not. Now it is harder to introduce healthy non-preferred foods and reduce junk foods.</td>
<td>1</td>
<td>Getting to know you</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>Monitoring &amp; limiting sweet, salty, high fat snacks and sugared beverages</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
<td>Healthy family meals &amp; encouraging picky eaters</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4</td>
<td>Matching amount/timing of food to child’s needs</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>Fatigue after treatment, problems with balance or ankle strength can make children feel frustrated by physical activity or more hesitant to engage.</td>
<td>5</td>
<td>Monitoring &amp; rewarding physical activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6</td>
<td>Overcoming obstacles to child physical activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>Making every day an active day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>Mid-way check-in/progress review</td>
</tr>
<tr>
<td>Screen Time</td>
<td>Screen time was helpful during hospital stays, medical visits, and as distraction from pain/nausea. Limits may not have been placed.</td>
<td>10</td>
<td>Monitoring screen time &amp; limit setting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12</td>
<td>Creating screen-free zones at home</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>Alternatives to screen time</td>
</tr>
<tr>
<td>Sleep Hygiene</td>
<td>Bedtime routines and sleep patterns disrupted by treatment. Problems with sleep efficiency and nighttime awakenings.</td>
<td>16</td>
<td>Establishing &amp; adhering to bedtime routines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18</td>
<td>Managing bedtime resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>20</td>
<td>Managing nighttime awakenings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22</td>
<td>Keeping your family on course</td>
</tr>
</tbody>
</table>

*Sequence of topics varies with the exception of weeks 1, 8, and 22*
To evaluate the impact of aerobic training intervention on fitness, neurocognitive function, physical performance, fatigue and quality of life in children with medulloblastoma.
Assessment

- Cogstate
- BRIEF
- PedsQL
- CPET
- Resting Energy Expenditure
- Hand Grip
- Sit and Reach
- Ankle Range of Motion
- BOT subtests 4-8
  - Bilateral Coordination, Balance, Running Speed and Agility, Upper-Limb Coordination, and Strength
Group Assignment

• Intervention
  – Physical Therapy (PT) 3 days/wk for 60 min for 6 weeks
  – Spend at least 30 min in target heart rate zone (55-65% of heart rate reserve)
  – Any functional activity to maintain target heart rate zone
  – Continued at home for 4-6 weeks during “break” prior to T2 assessment

• Control
  – Traditional PT
82 children with medulloblastoma
- 49% high risk disease
- 61% male
- 48% ≤age 10 years

Randomized
- 37 aerobic training+PT
- 45 PT

Mean increase peak oxygen uptake
- Aerobic training+PT 1.62 ml/kg/min
- PT -0.49 ml/kg/min.
The association between peak oxygen uptake and both psychomotor function and working memory were significant at the end of the intervention. There was also an effect of group assignment for the psychomotor task.
Pre-habilitation intervention for children with extremity sarcoma

Aims

• To determine if individuals diagnosed with a malignancy of the LE can participate in a 10-week preoperative exercise regimen

• To evaluate the impact of preoperative exercise training on function at 10-12 weeks postoperatively

• To compare these individuals to historical controls who did not receive regularly scheduled PT intervention prior to surgery

Design

• Pre-intervention Initial Evaluation

• 10 weeks of preoperative PT including strengthening, endurance exercise, and stretching

• Evaluation just prior to limb sparing or amputation

• 10-12 weeks of postoperative PT

• Post-intervention Evaluation

Corr 2017 Rehabil Oncol
## Study Population

<table>
<thead>
<tr>
<th></th>
<th>Intervention (N=14)</th>
<th>Controls (N=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Non-white</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKA</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>BKA</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Hemipelvectomy</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Hip Disarticulation</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Limb sparing femur</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Limb sparing tibia/fibula</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>11</td>
<td>35</td>
</tr>
<tr>
<td>Ewing Sarcoma</td>
<td>2</td>
<td>14.3</td>
</tr>
<tr>
<td>Chondroblastoma</td>
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<td>7.1</td>
</tr>
<tr>
<td>Age at diagnosis (Mean, SD) yrs.</td>
<td>13.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>
Results

• **Feasibility**
  - 12 of 14 patients completed at least 50% of scheduled physical therapy appointments.
  - Participants had difficulty completing the timed up and go test and the timed up and down stairs at both baseline and post-surgery regardless of group.

• **Effects**
  - Range of motion and strength outcomes did not differ by group
  - FMA scores were higher/better in the intervention group
    • Pain
    • Functional mobility with two specific measures
    • Walking supports
    • Satisfaction with walking quality
    • Participation in work, school, sports
    • Endurance

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**FMA Total Score**

![Chart showing FMA Total Score with baseline, pre-surgery, and 10-12 weeks post surgery data for intervention and control groups.](Corr 2017 Rehabil Oncol)
Exercise with NAD$^+$ Precursor Supplementation for AYA HCT survivors

**Indirect Effects:**
inactivity, aging, poor nutrition

**Cancer Diagnosis**

**Direct Effects:**
chemotherapy (HCT conditioning), radiation, GvHD glucocorticoids

**Decline in Indices of Skeletal Muscle Health:**
mass, mitochondrial metabolism, strength, aerobic capacity

**Decline in Cardiovascular Reserve Capacity**

**Premature Mortality**

**Intervention:**
exercise + NAD$^+$ precursor supplement

(R01 CA254955 Mostoufi-Moab, McCormack)
NAD⁺ Precursors: Focus on NAD⁺

NR → NMN → NAD⁺

NRKs → NMNATs

Food intake
Endogenous production

Nicotinamide

NAMPT
• Randomized, placebo-controlled trial with a 2x2 factorial design testing the effects of an NAD$^+$ precursor (NR) and exercise on muscle mass/strength and VO$_2$max in HSCT survivors.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>NR alone</td>
<td>NR + Exercise</td>
<td>Placebo + Exercise</td>
<td>Placebo alone</td>
</tr>
</tbody>
</table>

• Outcomes
  – Muscle strength, muscle mass, VO$_2$peak, Muscle mitochondrial OXPHOS capacity (via Creatine Chemical Exchange Saturation Transfer MRI)
Intervention Components

- Nicotinamide Riboside (NR):
  - Tru Niagen ® 300 mg capsules
  - Dispensed by the Hospital of the University of Pennsylvania Investigational Drug Service (IDS).
- Matched Placebo

- Exercise Intervention:
  - 16--week exercise program
  - Each remote session monitored via Tele-health, HR
  - Personalized exercise plan
    - Stationary bicycle
    - Weights
Summary

- Accelerated aging is prevalent among childhood cancer survivors characterized by:
  - Disease and deficit accumulation
  - Physiologic phenotype
  - Molecular markers of aging

- Interventions are underway to remediate frail health.
  - Targeting disease and deficit accumulation
  - Targeting components of physiologic phenotype
  - Targeting molecular aging

- Interventions are underway/planned to prevent frail health soon after or during therapy in children with cancer.
Thank you!

- I am happy to take questions now or later via e-mail (kiri.ness@stjude.org).