CCSS
Childhood Cancer
Survivor Study

Psychology Working Group

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St. Jude Children's
Research Hospital

An NCI-funded Resource

Scope of Research

Outcomes and interventions involving:

- Neurocognitive function
  - Neurocognitive questionnaire, CNS Vital Signs
- Psychosocial function
  - Emotional distress, pain, sleep
  - Social attainment
  - Functional independence
- Health-related quality of life
  - SF-36

Working Group Membership

Name	Discipline	Institution
Pim Brouwers	Neuroscience	National Institute of Mental Health
Austin Brown	Epidemiology	Baylor College of Medicine
Lauren Daniel	Psychology	Rutgers University
Kim Edelstein	Neuropsychology	Princess Margaret Cancer Center
Bob Hayashi	Pediatric Oncology	Washington University – St. Louis
Tricia King	Neuropsychology	Emory University
Kevin Krull*	Neuropsychology	St. Jude Children's Research Hospital
Jordan Marchak	Psychology	Emory University
Rachel Peterson	Neuropsychology	Kennedy Krieger Institute/Johns Hopkins University
Kathy Ruble	Nursing	Johns Hopkins University
Satomi Sato	Clinical Psychology	St. Luke's International University, Japan
Fiona Schulte	Psychology	University of Calgary
Lindsay Schwartz	Pediatric Oncology	University of Chicago
Derek Tsang	Radiation Oncology	Princess Margaret Cancer Center
Emily Walling	Pediatric Oncology	University of Michigan
Megan Ware	Health Behavior	University of North Texas
Christopher Weldon	Surgery	Harvard University
AnnaLynn Williams	Epidemiology	University of Rochester

Working Group Progress

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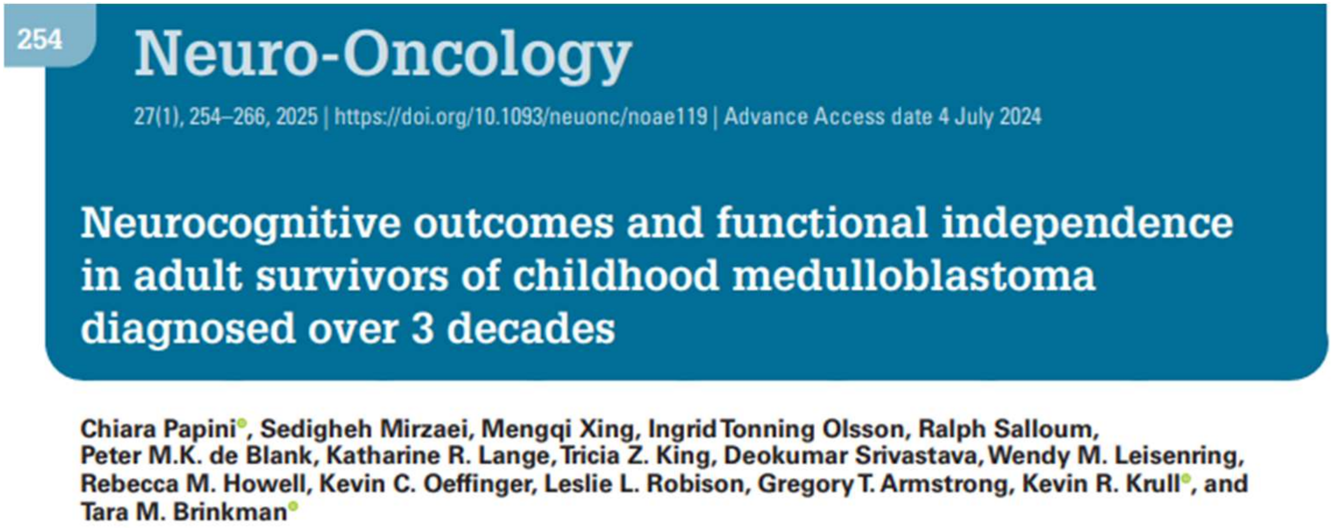
11	Published/In Press Manuscripts (since 1/1/2023)
3	Currently Submitted Manuscripts
18	Analysis/Manuscript in Process
4	Concepts in development
5	New AOIs (total, since 1/1/2023)

Highlights of Recently Completed Research



254
Neuro-Oncology
27(1), 254–266, 2025 | https://doi.org/10.1093/neuonc/noae119 | Advance Access date 4 July 2024

Neurocognitive outcomes and functional independence in adult survivors of childhood medulloblastoma diagnosed over 3 decades

Chiara Papini, Sedigheh Mirzaei, Mengqi Xing, Ingrid Tonning Olsson, Ralph Salloum, Peter M.K. de Blank, Katharine R. Lange, Tricia Z. King, Deokumar Srivastava, Wendy M. Leisenring, Rebecca M. Howell, Kevin C. Oeffinger, Leslie L. Robison, Gregory T. Armstrong, Kevin R. Krull, and Tara M. Brinkman

Highlights of Recently Completed Research

Papini et al., Medulloblastoma outcomes.
Neuro-Oncology, 2024

Historical therapy: surgery + CSI ≥ 30Gy, without chemotherapy (n=55)

High-risk multimodal therapy: surgery + CSI ≥ 30Gy + chemotherapy (n=186)

Standard-risk multimodal therapy: surgery + CSI > 0 to < 30Gy + chemotherapy (n=120)

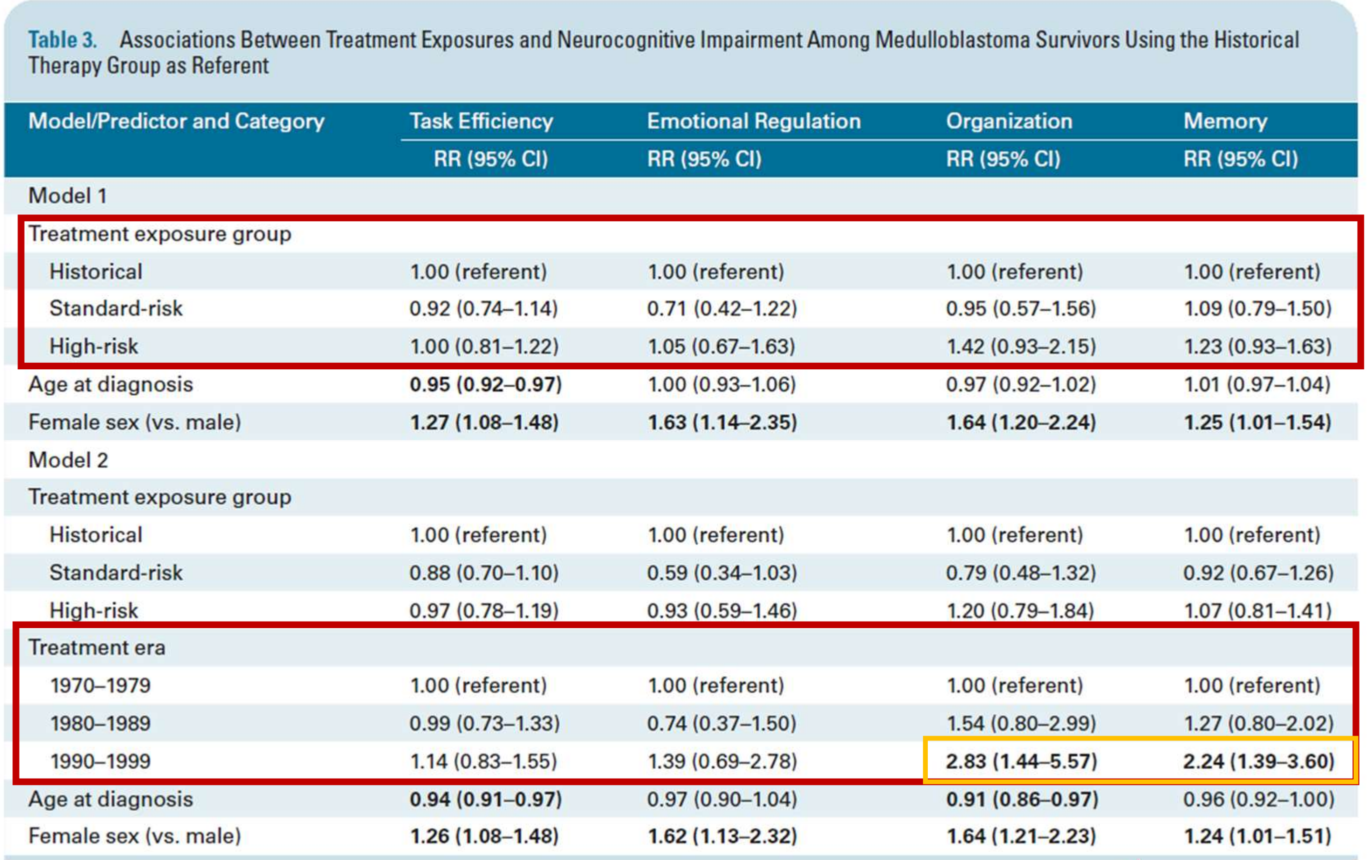


Table 3. Associations Between Treatment Exposures and Neurocognitive Impairment Among Medulloblastoma Survivors Using the Historical Therapy Group as Referent

Model/Predictor and Category	Task Efficiency	Emotional Regulation	Organization	Memory
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Model 1				
Treatment exposure group				
Historical	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Standard-risk	0.92 (0.74–1.14)	0.71 (0.42–1.22)	0.95 (0.57–1.56)	1.09 (0.79–1.50)
High-risk	1.00 (0.81–1.22)	1.05 (0.67–1.63)	1.42 (0.93–2.15)	1.23 (0.93–1.63)
Age at diagnosis	**0.95 (0.92–0.97)**	1.00 (0.93–1.06)	0.97 (0.92–1.02)	1.01 (0.97–1.04)
Female sex (vs. male)	**1.27 (1.08–1.48)**	**1.63 (1.14–2.35)**	**1.64 (1.20–2.24)**	**1.25 (1.01–1.54)**
Model 2				
Treatment exposure group				
Historical	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Standard-risk	0.88 (0.70–1.10)	0.59 (0.34–1.03)	0.79 (0.48–1.32)	0.92 (0.67–1.26)
High-risk	0.97 (0.78–1.19)	0.93 (0.59–1.46)	1.20 (0.79–1.84)	1.07 (0.81–1.41)
Treatment era				
1970–1979	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1980–1989	0.99 (0.73–1.33)	0.74 (0.37–1.50)	1.54 (0.80–2.99)	1.27 (0.80–2.02)
1990–1999	1.14 (0.83–1.55)	1.39 (0.69–2.78)	**2.83 (1.44–5.57)**	**2.24 (1.39–3.60)**
Age at diagnosis	**0.94 (0.91–0.97)**	0.97 (0.90–1.04)	**0.91 (0.86–0.97)**	0.96 (0.92–1.00)
Female sex (vs. male)	**1.26 (1.08–1.48)**	**1.62 (1.13–2.32)**	**1.64 (1.21–2.23)**	**1.24 (1.01–1.51)**

Highlights of Recently Completed Research

Papini et al., Medulloblastoma outcomes. *Neuro-Oncology, 2024*

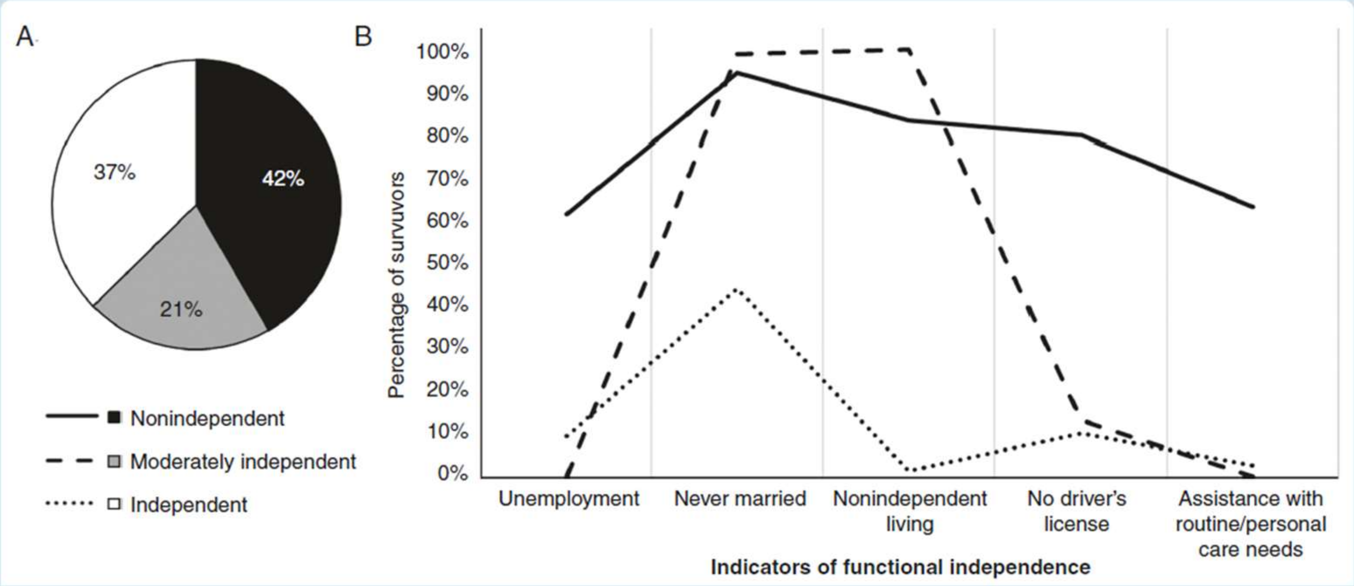


Figure 1. Classes of functional independence among adult survivors of childhood medulloblastoma, obtained through latent class analysis. (A) Percentage of the whole sample categorized in each class of functional independence. (B) Percentage of survivors with a negative outcome on the 5 indicators of functional independence in each class.

Risk factors for non-Independence:

Impaired task efficiency **(RR: 1.93)**

Chronic Health Conditions:

Sensory-motor **(RR:1.24)**

Hearing **(RR:1.28)**

Seizures/epilepsy **(RR:1.54)**

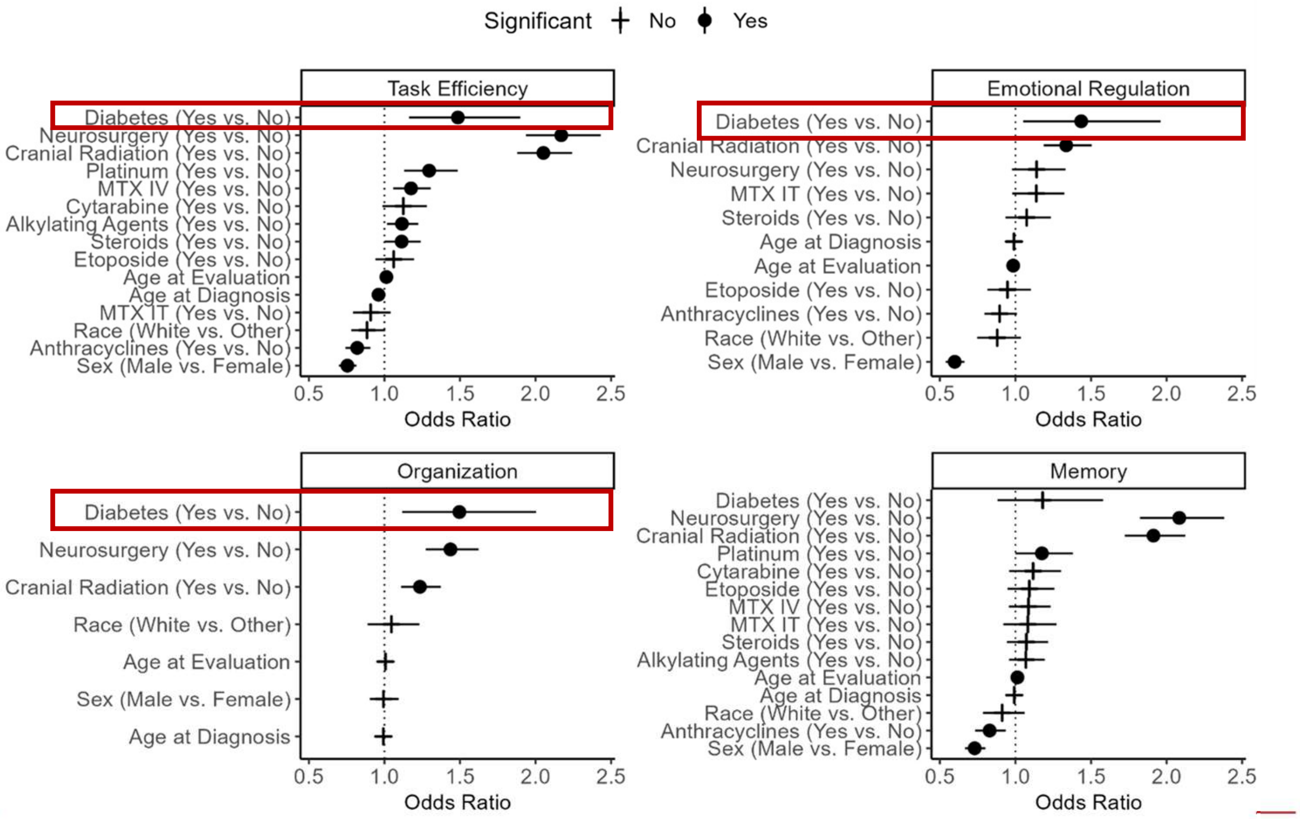
Highlights of Recently Completed Research

Webster et al., Diabetes and neurocognition (*under review*).

N = 16,196

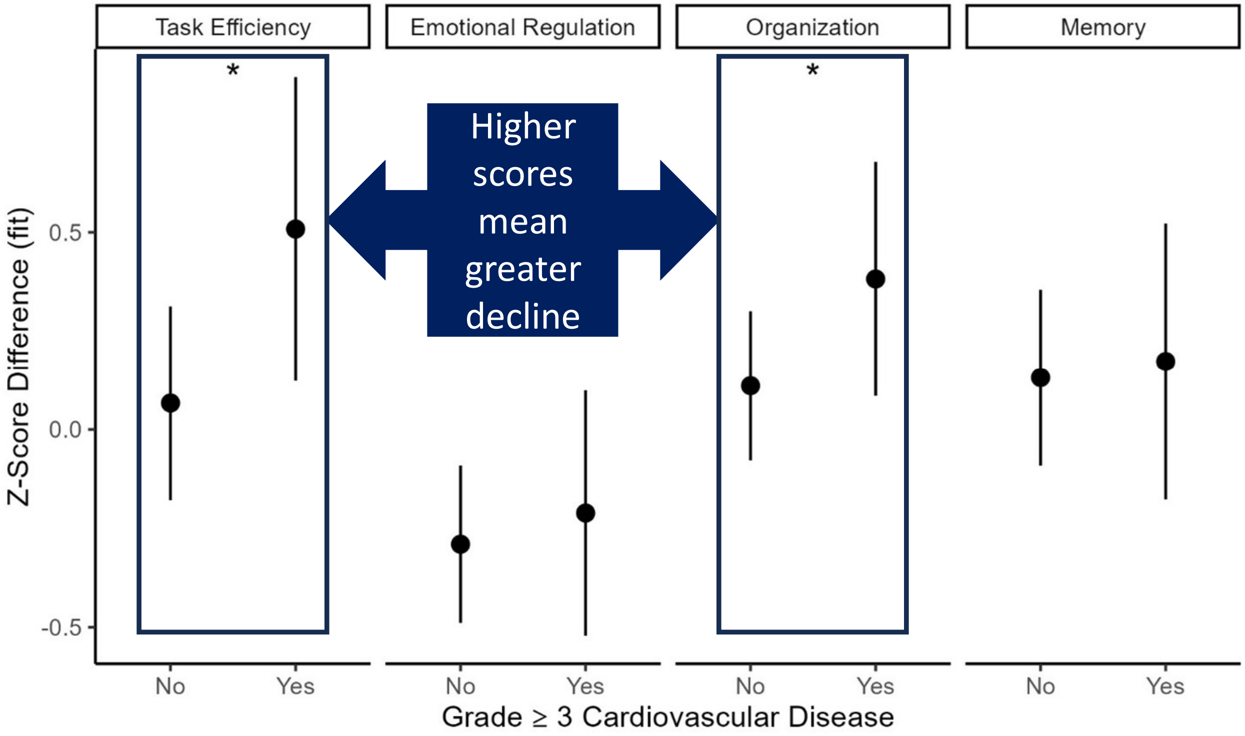
615 diabetes mellitus

36 years of age



Highlights of Recently Completed Research

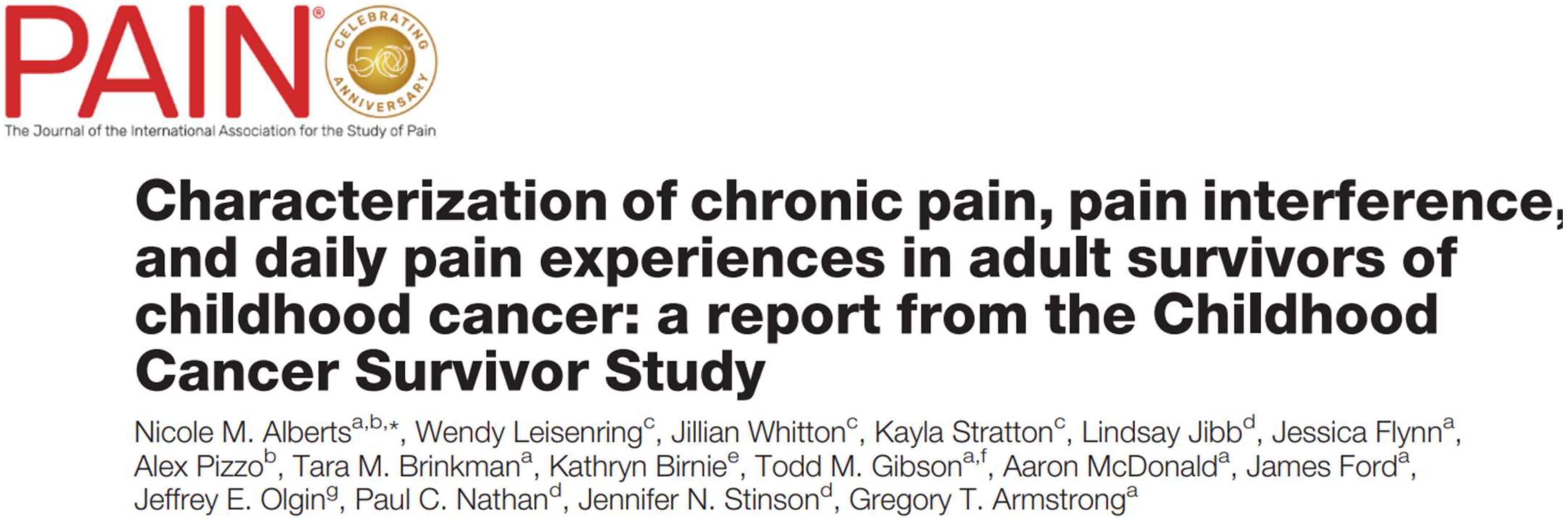
Webster et al., Diabetes and neurocognition (*under review*).



Higher scores mean greater decline

Highlights of Recently Completed Research

CCSS



PAIN®
CELEBRATING 50th ANNIVERSARY
The Journal of the International Association for the Study of Pain

Characterization of chronic pain, pain interference, and daily pain experiences in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study

Nicole M. Alberts[a,b,*], Wendy Leisenring[c], Jillian Whitton[c], Kayla Stratton[c], Lindsay Jibb[d], Jessica Flynn[a], Alex Pizzo[b], Tara M. Brinkman[a], Kathryn Birnie[e], Todd M. Gibson[a,f], Aaron McDonald[a], James Ford[a], Jeffrey E. Olgin[g], Paul C. Nathan[d], Jennifer N. Stinson[d], Gregory T. Armstrong[a]

Highlights of Recently Completed Research

CCSS

Alberts et al., Characterization of chronic pain. *Pain, 2024.*

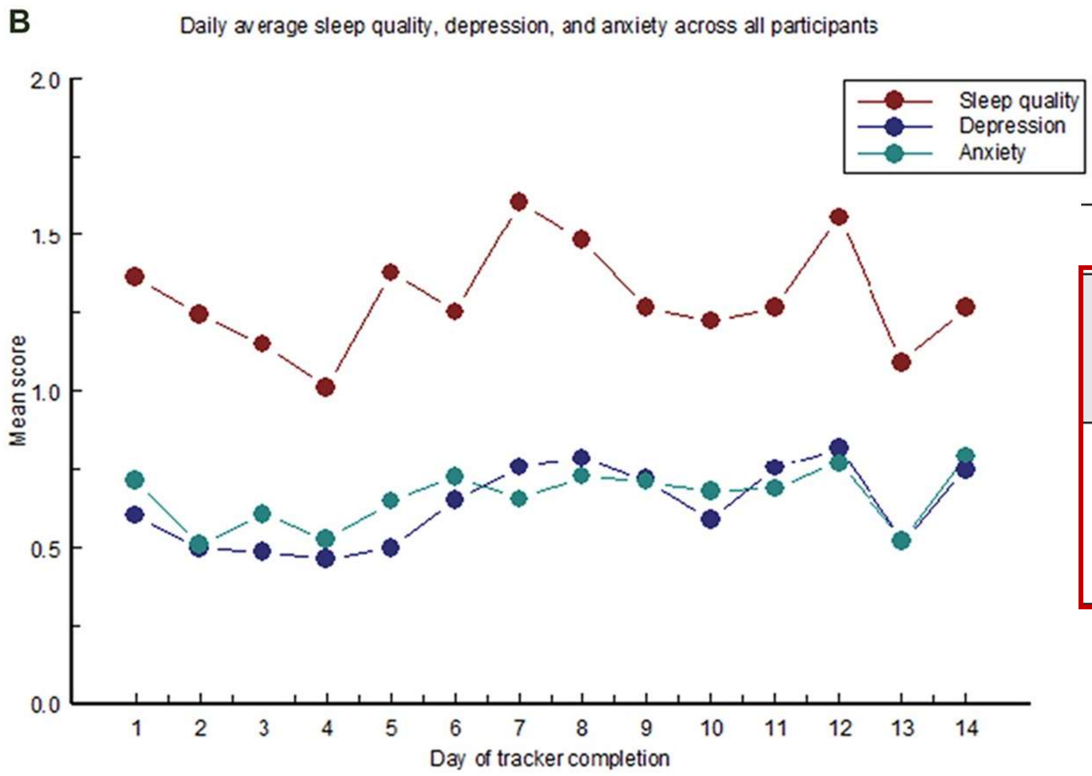
≥3 months of persistent/recurrent pain

n = 233	N (%)
Female	118 (50.6)
White Non-Hispanic	207 (88.8)
Diagnosis	
Leukemia	79 (33.9)
CNS tumor	24 (10.3)
Hodgkin lymphoma	24 (10.3)
Non-Hodgkin lymphoma	24 (10.3)
Bone cancer	29 (12.4)
Other	53 (22.8)
	Mean (SD)
Age at evaluation	40.8 (9.0)
Time since diagnosis	32.5 (7.9)

- 41% reported chronic pain
- 32% had pain for more than 10 years
- 64% moderate to severe pain intensity
- 76% moderate to severe pain interference
- 30% moderate to severe anxiety
- 40% moderate to severe depression

Highlights of Recently Completed Research

Alberts et al., Characterization of chronic pain. *Pain, 2024.*

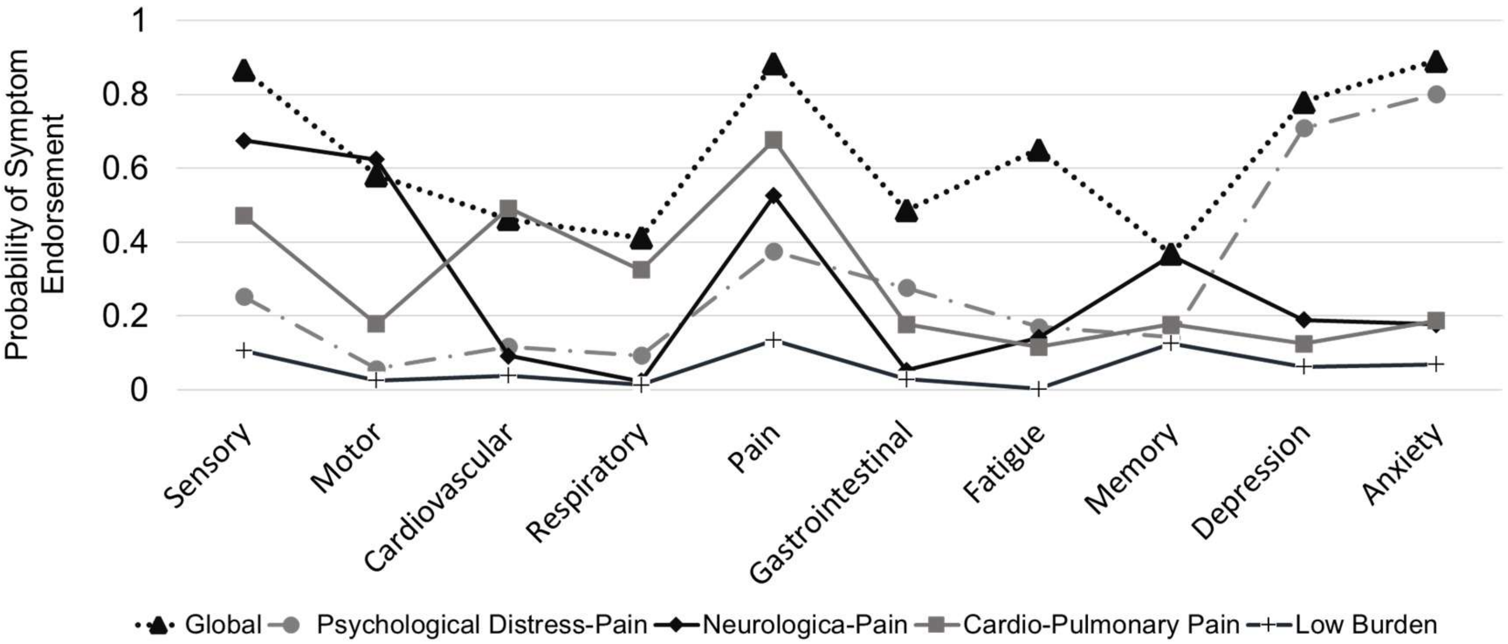


	Male		
	B	95% CI	*P*
Pain intensity			
Sleep quality	0.4	0.1, 0.6	0.004
Anxiety	0.3	0.1, 0.5	0.003
Elevated anxiety (≥3)*	0.8	0.1,1.5	0.03
Depressive symptoms	0.3	0.1, 0.4	0.009
Pain interference			
Elevated pain intensity (≥5)†	2.1	1.4, 2.8	<0.0001
Sleep quality	0.3	0.0, 0.7	0.03
Anxiety	0.2	0.0, 0.5	0.047
Depressive symptoms	0.4	0.2, 0.6	<0.001
Elevated depressive symptoms (≥3)*	1.3	0.6, 2.1	<0.001

Highlights of Recently Completed Research

Webster et al., Symptom burden, healthcare use and health behaviors (*under review*).

N = 17,237 survivors



Low burden: 63%

Distress-pain: 13%

Neurologic-pain: 11%

Cardiopulmonary-pain: 5%

Global burden: 8%

Highlights of Recently Completed Research

CCSS

Webster et al., Symptom burden, healthcare use and health behaviors (*under review*).

Phenotype	**Key characteristics**	**Associated risks**	**Suggested interventions**
Low burden	Few or no symptoms	↓ Poor health behaviors ↓ Healthcare use	Standard f/u care (SFU)
Psychological distress-Pain	Pain, depression, and anxiety	↑ Smoking ↑ Physical inactivity ↑ Emergency room use	SFU + mental health support, pain management
Cardiopulmonary-Pain	Sensory, cardiac, respiratory, and pain	↑ Smoking ↑ Physical inactivity	SFU + exercise, heart health strategies, pain management
Neurologic-Pain	Sensory, motor, pain, and memory problems	↑ Physical inactivity ↑ BMI ↑ Emergency room use	SFU + exercise, cognitive support, pain management
Global	Sensory, motor, cardiac, respiratory, pain, depression, and anxiety	↑ Healthcare use ↑ Health behavior risk	Comprehensive interdisciplinary care

Ancillary Studies

MPIs: Tara Brinkman and Kevin Krull (St. Jude Children's Research Hospital)

Title: Impact of eHealth intervention for insomnia on late effects of childhood cancer

Funding Source: National Cancer Institute (R01); $4,271,243

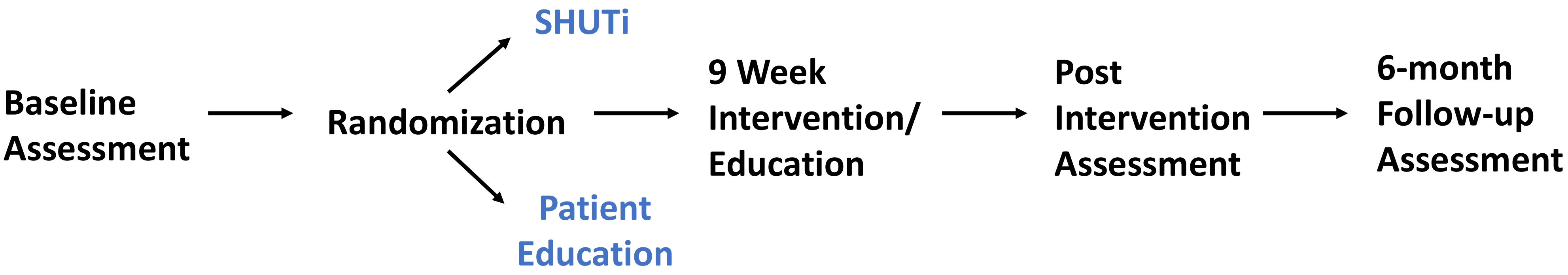
Aims:

1. To examine the <u>efficacy of an eHealth intervention for improving symptoms of insomnia</u> among adult survivors of childhood cancer
2. To determine whether <u>treatment of insomnia will improve neurocognitive function</u> in adult survivors of childhood cancer with both insomnia and neurocognitive impairment
3. To explore the mediating effects of improved neurocognitive function, emotional distress, and cardiovascular health on the association between insomnia symptoms and quality of life

Ancillary Studies

Randomized clinical trial (not blinded)

9-week intervention with 6-month follow-up



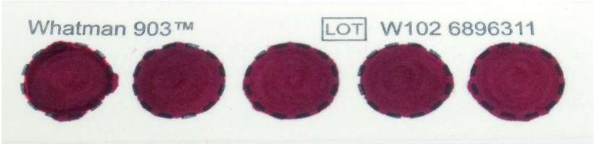
Ancillary Studies

CCSS

Outcome	Assessment Method
Insomnia Symptoms	• Insomnia Severity Index • Daily Sleep Diary • Actigraphy (WHOOP)
Neurocognitive Function	• CNS Vital Signs • CCSS Neurocognitive Questionnaire
Emotional Health	• PHQ-9
Quality of Life	• SF-36
Cardiovascular Health	• Physical activity (WHOOP) • Heart rate variability (WHOOP) • Dried Blood Spot Cards: – Inflammation – Oxidative stress – Vascular function – Lipid profiles

WHOOP UNITE

CNS Vital Signs



Ancillary Studies

Eligible
n = 541

Initiated study activities
n = 464 (86%)

9 weeks post-intervention
n = 347 (75%)

6 months post-intervention
n = 305 (66%)

	Control (n = 268)	Treatment (n = 273)
Age at enrollment		
Median (min-max)	43.3 (22.8-65.3)	44.8 (25.7-65.7)
Time since diagnosis		
Median (min-max)	36.4 (21.9-52.8)	37.4 (21.9-52.9)
Sex, n (%)		
Female	198 (73.88)	197 (72.16)
Race/Ethnicity, n (%)		
Non-Hispanic White	226 (84.33)	232 (84.98)
Diagnosis, n (%)		
Leukemia	100 (37.31)	102 (37.36)
Hodgkin disease	30 (11.19)	43 (15.75)
Non-Hodgkin lymphoma	25 (9.33)	24 (8.79)
Bone tumor	31 (11.57)	32 (11.72)
Kidney tumor	42 (15.67)	33 (12.09)
Neuroblastoma	21 (7.84)	23 (8.42)
Soft tissue sarcoma	19 (7.09)	16 (5.86)

Ancillary Studies

Preliminary Results:

Insomnia Severity Index

	Baseline to 9 weeks		**Baseline to 6 months**	
	Control	Treatment	Control	Treatment
Mean change score	-2.54	-5.05	-2.45	-5.75
Effect Size (Cohen's d)	**0.58**		**0.74**	

New Ancillary Studies

Title: Internet-delivered cognitive behavioral therapy to improve chronic pain and frailty in survivors of childhood cancer

PI: Tara Brinkman (St. Jude Children's Research Hospital); R01

Aims:

1. Evaluate the efficacy of Internet-delivered cognitive behavior therapy (ICBT) vs. attention control (online pain education) for improving pain interference among adult survivors of childhood cancer with chronic pain who are pre-frail or frail
2. Examine the impact of ICBT on components of frailty
3. Determine whether ICBT impacts symptom multimorbidities, functional outcomes, and opioid use

Exploratory: 1) Examine associations between biomarkers of physiologic activity and changes in pain and frailty post-intervention and at 6-month follow-up 2) Determine whether baseline clinical characteristics including mood, anxiety-related factors, and sleep moderate the effect of ICBT on pain and frailty

New Ancillary Studies

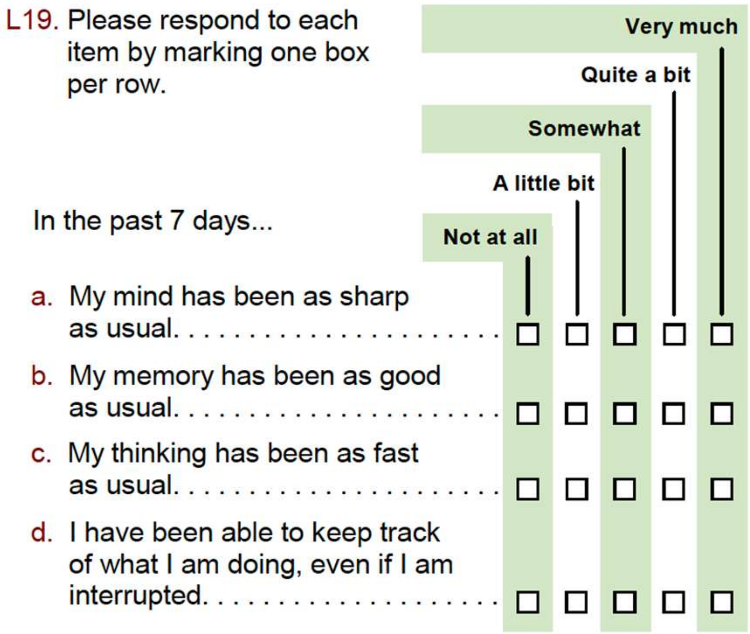
Title: Effects of a virtual mind-body resilience program to improve coping and resilience among childhood, adolescent and young adult survivors

PI: Giselle Perez (Harvard/Mass General); R01

Aims:

1. Determine the effectiveness of two digital resilience interventions (SMART-3RP-S and SMART-3RP-A) for improving resilience (<u>primary outcome</u>) among CAYA survivors
2. To explore moderators (e.g., age, race/ethnicity, language, zip code, cancer/medical history, baseline distress) of the intervention effect on resilience at 6 and 12 months
3. Apply a mixed methods design to assess intervention reach, engagement, acceptability, fidelity, sustainability

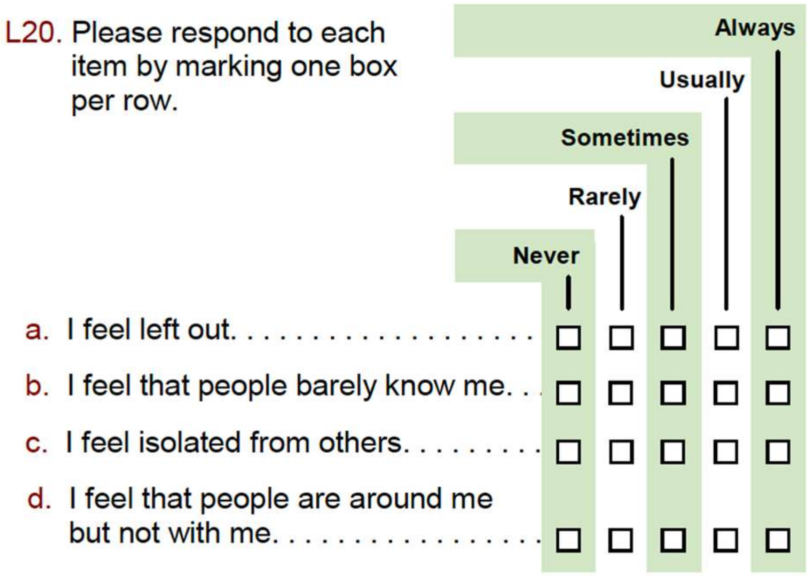
Plan to Utilize FU7 Newly Frozen Data…



L19. Please respond to each item by marking one box per row.

In the past 7 days...

	Not at all	A little bit	Somewhat	Quite a bit	Very much
a. My mind has been as sharp as usual.	☐	☐	☐	☐	☐
b. My memory has been as good as usual.	☐	☐	☐	☐	☐
c. My thinking has been as fast as usual.	☐	☐	☐	☐	☐
d. I have been able to keep track of what I am doing, even if I am interrupted.	☐	☐	☐	☐	☐



L20. Please respond to each item by marking one box per row.

	Never	Rarely	Sometimes	Usually	Always
a. I feel left out.	☐	☐	☐	☐	☐
b. I feel that people barely know me.	☐	☐	☐	☐	☐
c. I feel isolated from others.	☐	☐	☐	☐	☐
d. I feel that people are around me but not with me.	☐	☐	☐	☐	☐

Plan to Utilize FU7 Newly Frozen Data…

Ongoing:

- Deficit accumulation index (Williams/Krull). Analyses ongoing. ISLCCC oral presentation
- Longitudinal patterns and predictors of cancer fears in survivors of childhood cancer (Tutelman/Schulte). Analyses recently completed. CCSS Trainee Award
- The impact of sleep trajectories on neurocognitive functioning in adult survivors of childhood cancer (Papini/Brinkman). Analyses recently completed. CCSS Trainee Award; ISLCCC oral presentation

New Proposals:

- Impact of social isolation on perceived cognitive changes (Paes/Brinkman). Proposal in development.
- Pain trajectories and social isolation/loneliness (Argenbright/Brinkman). Proposal in development.
- Impact of physical activity and psychological distress on neurocognitive function over time (Sharkey/van der Plas). Proposal in development. CCSS Trainee Award

Plan for Concept Development Using FU8 Survey Data Focused on Aging…

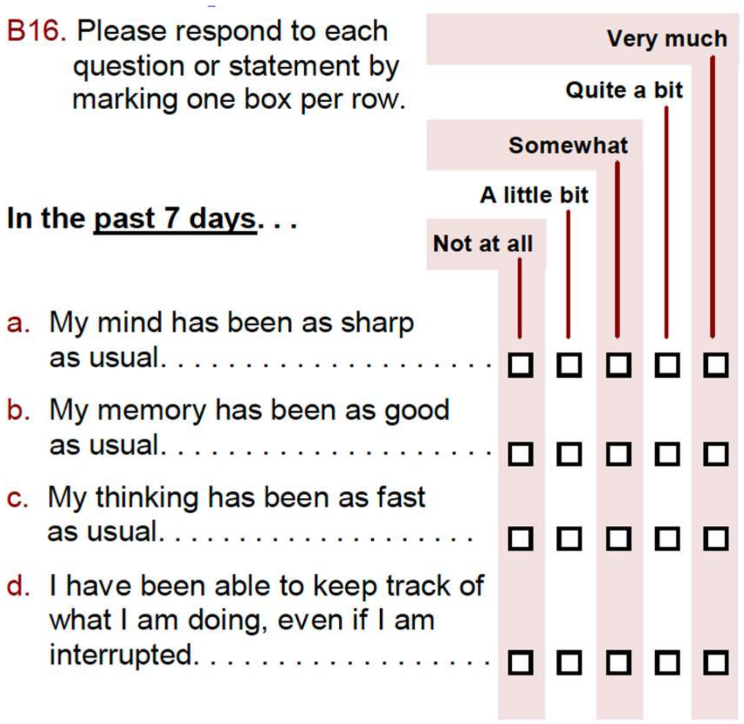
CCSS

<u>CNS Vital Signs</u> – Computerized Cognitive Assessment

Verbal memory, visual memory, processing speed, executive function

<u>Questions:</u>

1. Baseline CNS-VS and perceived cognitive function
2. Change in objective function over time (FU9)
3. Change in objective function and perceived change
4. Change in perceived change over time (FU9)



B16. Please respond to each question or statement by marking one box per row.

In the <u>past 7 days</u>. . .

	Not at all	A little bit	Somewhat	Quite a bit	Very much
a. My mind has been as sharp as usual.	☐	☐	☐	☐	☐
b. My memory has been as good as usual.	☐	☐	☐	☐	☐
c. My thinking has been as fast as usual.	☐	☐	☐	☐	☐
d. I have been able to keep track of what I am doing, even if I am interrupted.	☐	☐	☐	☐	☐

Plan for Concept Development Using FU8 Survey Data Focused on Aging…

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New Proposals:

- Remote neurocognitive assessment – feasibility and validity in CCSS (van der Plas/Krull). Proposal in development.
- Memory problems in aging survivors of childhood cancer (Brinkman/Krull). Proposal in development.

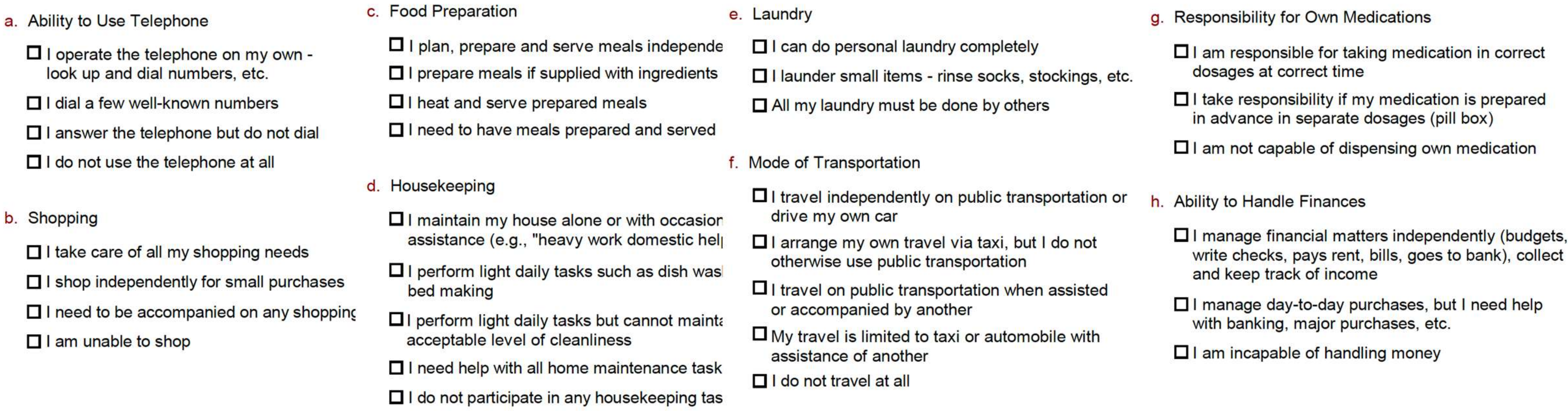
Plan for Concept Development Using FU8 Survey Data Focused on Aging…

CCSS

Additional Questions:

Neurocognitive and psychosocial predictors of instrumental activities of daily living

- Shopping, food prep, housekeeping, laundry, transportation, medication use, ability to handle finances



a. Ability to Use Telephone

☐ I operate the telephone on my own - look up and dial numbers, etc.
☐ I dial a few well-known numbers
☐ I answer the telephone but do not dial
☐ I do not use the telephone at all

b. Shopping

☐ I take care of all my shopping needs
☐ I shop independently for small purchases
☐ I need to be accompanied on any shoppinç
☐ I am unable to shop

c. Food Preparation

☐ I plan, prepare and serve meals independe
☐ I prepare meals if supplied with ingredients
☐ I heat and serve prepared meals
☐ I need to have meals prepared and served

d. Housekeeping

☐ I maintain my house alone or with occasion assistance (e.g., "heavy work domestic hel
☐ I perform light daily tasks such as dish was bed making
☐ I perform light daily tasks but cannot mainta acceptable level of cleanliness
☐ I need help with all home maintenance task
☐ I do not participate in any housekeeping tas

e. Laundry

☐ I can do personal laundry completely
☐ I launder small items - rinse socks, stockings, etc.
☐ All my laundry must be done by others

f. Mode of Transportation

☐ I travel independently on public transportation or drive my own car
☐ I arrange my own travel via taxi, but I do not otherwise use public transportation
☐ I travel on public transportation when assisted or accompanied by another
☐ My travel is limited to taxi or automobile with assistance of another
☐ I do not travel at all

g. Responsibility for Own Medications

☐ I am responsible for taking medication in correct dosages at correct time
☐ I take responsibility if my medication is prepared in advance in separate dosages (pill box)
☐ I am not capable of dispensing own medication

h. Ability to Handle Finances

☐ I manage financial matters independently (budgets, write checks, pays rent, bills, goes to bank), collect and keep track of income
☐ I manage day-to-day purchases, but I need help with banking, major purchases, etc.
☐ I am incapable of handling money

Opportunities for Collaboration with Other Working Groups

- Evaluation of the impact of physical co-morbidities on psychological outcomes (**Chronic Disease**)
- Impact of psychological function on health behaviors and health care utilization (**Cancer Control and Intervention**)
- Identification of how genetic moderators of cancer therapy impact psychological outcomes (**Genetics**)
- Machine learning approaches to identify predictors of psychological outcomes; psychometric properties and sensitivity of current measures (**Epi/Biostats**)

As CCSS Engages with Participants This Year What Would You Like to Learn From Them?

- Exposure, diagnosis, treatment related to COVID; potential long-term impact of COVID (i.e., long COVID)
- Social supports currently available to survivors
- Input and observations from significant others (i.e., dementia; scope of outcomes)

Value Added to Your Working Group by a 2000-2025 Cohort Expansion

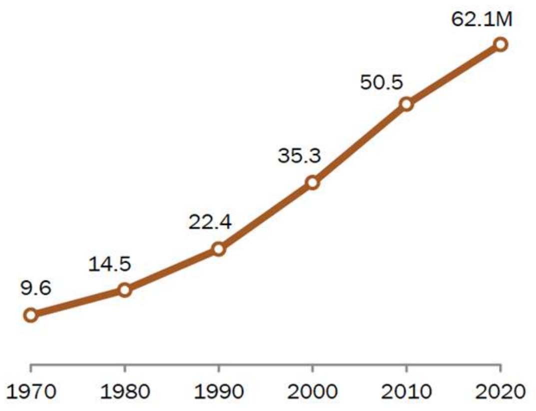
CCSS

- Neurocognitive impact of contemporary treatment exposures
- Psychosocial adjustment with more modern supportive cancer care
- Outcomes/expectations in Gen Y (millennials), **Gen Z**, Gen A
- Enhanced diversity in survivor characteristics
- Potential access to parents/caregivers

Special Considerations for a Cohort Expansion Specific to Your Working Group

CCSS

Representativeness of social characteristics/health determinants



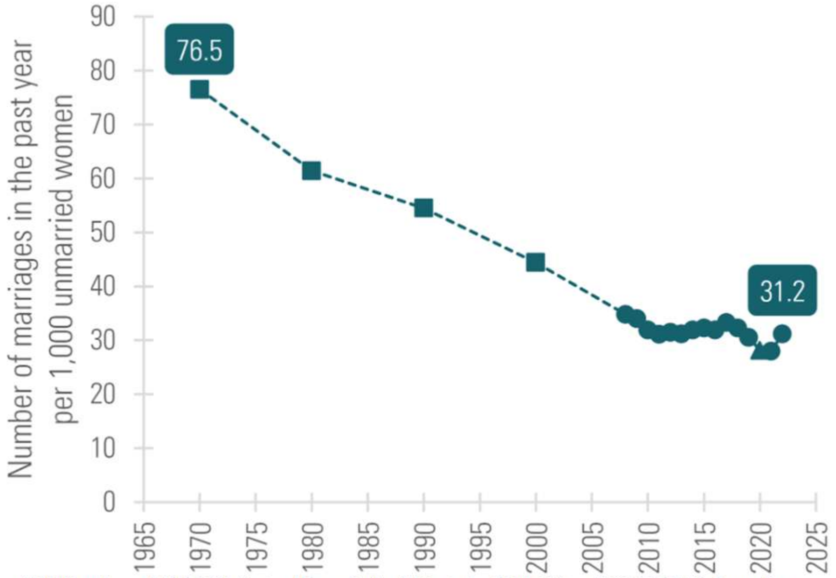
U.S. Hispanic population reached more than 62 million in 2020

In millions

Note: Population totals are as of April 1 each year. Hispanics are of any race.
Source: Pew Research Center analysis of 1970-1980 estimates based on decennial censuses (see 2008 report "U.S. Population Projections: 2005-2050"), 1990-2020 PL94-171 census data.

Consideration of social changes

Figure 1. Women's Adjusted Marriage Rate, 1970-2022



Source: NCFMR analyses of 1970-2000, National Center for Health Statistics; 2008-2019 and 2021-2022, U.S. Census Bureau, American Community Survey, 1-yr est., and 2020 American Community Survey, 1-year Experimental PUMS

Special Considerations for a Cohort Expansion Specific to Your Working Group

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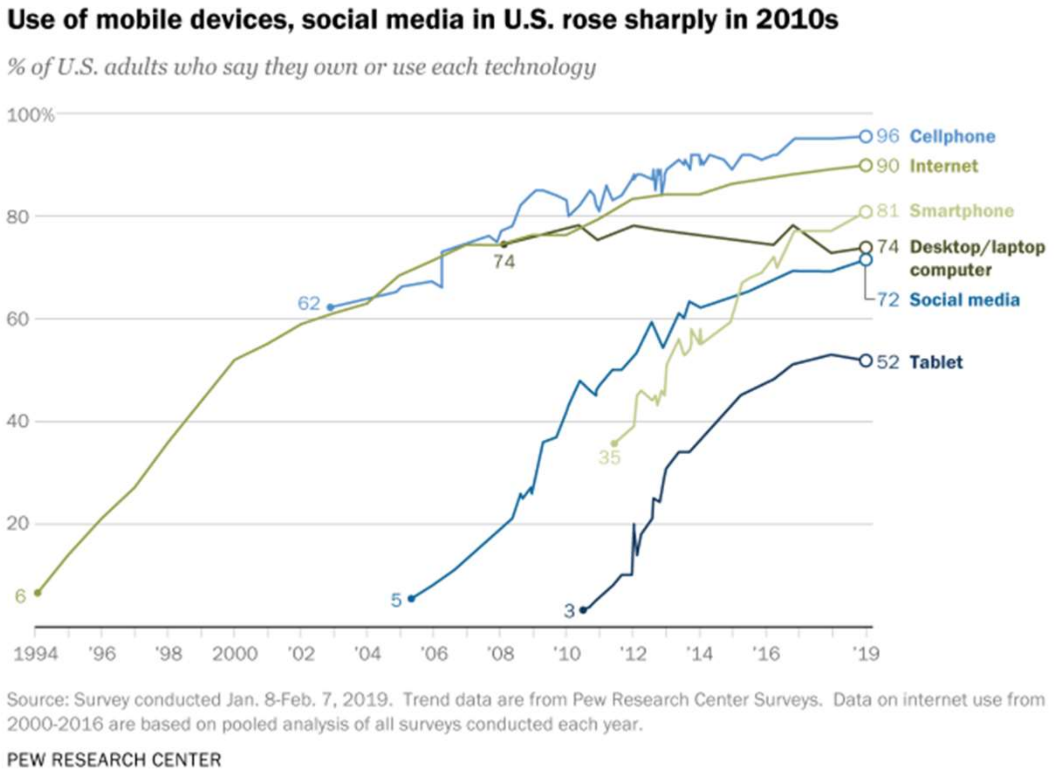

Use of mobile devices, social media in U.S. rose sharply in 2010s

% of U.S. adults who say they own or use each technology

Source: Survey conducted Jan. 8-Feb. 7, 2019. Trend data are from Pew Research Center Surveys. Data on internet use from 2000-2016 are based on pooled analysis of all surveys conducted each year.

PEW RESEARCH CENTER

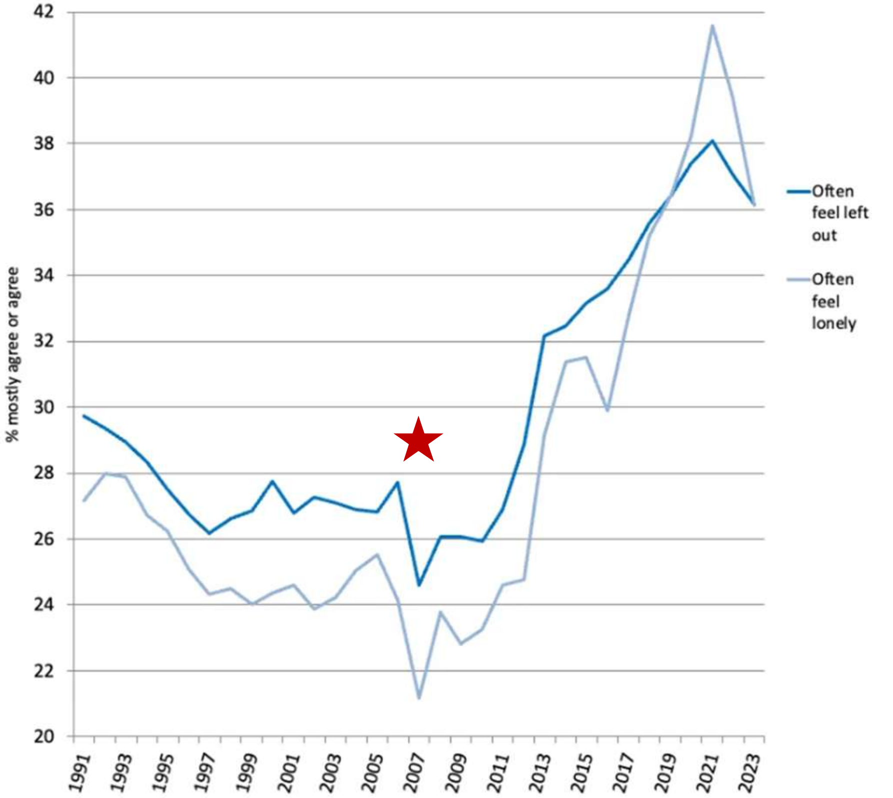

Figure 1: Percent of U.S. teens who agree that they often feel left out or often feel lonely, 1991-2023. Source: Monitoring the Future

Five Year Plan: Progress Update

1. Remotely delivered cognitive behavioral therapy to treat emotional distress, pain and pain related disability, and sleep/fatigue
2. Remotely delivered psychoeducation, behavioral, and cognitive interventions to facilitate improvement and adaption to neurocognitive deficits
3. Evaluate impact of cancer and cancer-directed therapies on directly assessed neurocognitive function in aging survivors

Current Top Priorities: One-Year Deliverables

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- Publication of ancillary study/clinical trial outcomes (i.e., SLEEPWELL)
- Complete analyses of initial CNS Vital Signs projects focused on objective assessment of cognitive aging
- Development of additional ancillary intervention projects

Discussion: Opportunities and Threats

CCSS

Major Threat or Challenge:

- Focus on change over time limits room for innovation/growth in scope
- Limited scope of positive psychological outcomes
  - Resilience, hope, motivation
- Limited data on impact from COVID

Major Opportunity:

- Long-term impact on caregivers