

Study Title: Functional Independence, Social Isolation, and Activities of Daily Living in Adult Survivors of Pediatric Bone Sarcomas

Working Groups:

Primary: Psychology

Secondary: Chronic Disease

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Background and Rationale

Bone tumors constitute about 6% of all cancers in children; of these, osteosarcoma (OS) and Ewing sarcoma (ES) are the most common diagnoses, together accounting for 90% of all primary pediatric bone tumors.¹⁻⁴ A diagnosis of OS or ES, along with the required therapies, can confer significant morbidity and mortality. Survival following these diagnoses has improved significantly from 10-20% prior to the 1970s, when effective multiagent chemotherapy regimens were developed for both OS and ES, to 70-80% in the modern era.⁵ Currently, patients with OS or ES are treated with neoadjuvant chemotherapy followed by local control and adjuvant chemotherapy. Local control for OS primarily consists of surgical resection, while radiation therapy is an additional option for local control of ES given its radiosensitivity.⁶

Following the improvement of chemotherapeutic regimens for OS and ES and cross-sectional imaging modalities, limb salvage surgeries have become more feasible and now comprise >90% of local control surgeries. Surgical options for local control of upper and lower extremity bone sarcomas now include amputation or limb salvage surgeries, and rotationplasty can also be performed for lower extremity bone sarcomas. Studies have shown that limb salvage surgeries, in combination with effective neoadjuvant and adjuvant chemotherapy regimens, are safe and have local recurrence rates and disease-free survival comparable to those seen with amputation.^{7, 8} The long-term functional outcomes and quality of life for patients undergoing different surgical approaches continues to be evaluated but has been thus far limited by a lack of large cohort studies and a unified measure of function and functional independence.⁹⁻¹¹

The improved long-term survival of patients with OS and ES as well as improved limb salvage surgical techniques creates an opportunity to evaluate functional independence in the large CCSS cohort of survivors of pediatric bone sarcomas. Previous cross-sectional studies examined aspects of functional independence in isolation among bone tumor survivors, but how those indices co-occur and how they collectively change over time remains unclear.^{12, 13} In addition, we can correlate functional independence with other important outcomes such as social isolation, ability to conduct activities of daily living (ADLs), and frailty. There is evidence that survivors diagnosed with bone sarcomas and those treated with amputation or limb sparing surgeries have an increased risk of being lonely, experiencing pain that interferes with daily living, or demonstrating a frail/pre-frail phenotype.¹⁴⁻¹⁶ However, how functional independence and its changes over time impact social isolation, financial hardship, ADLs, frailty and health-related quality of life is unknown.

In this study, we propose to build upon the prior work done in identifying classes of functional and social independence in survivors of pediatric brain tumors in the SJLIFE¹⁷ and CCSS^{18, 19} cohorts and to expand this framework to survivors of bone sarcomas. These studies identified three classes of functional independence: independent, moderately independent, and non-independent using six observed indicators: independent living; marital status; ability to work or attend school/employment status; assistance with personal care needs; assistance with routine needs; and currently holding a driver's license. We will identify classes of functional independence for survivors of pediatric bone sarcomas and attempt to characterize change in class membership over time. We will also examine treatment exposures including surgical intervention and the presence of chronic health conditions and their associations with worsening function over time. Understanding patterns of functional independence and risk factors for non-independence, social isolation, financial hardship, difficulty performing ADLs, frailty and health-related quality of life in survivors of pediatric bone

sarcomas may further inform intervention strategies, supportive care measures, and the ability to better counsel patients and survivors.

Specific Aims and Hypotheses

Aim 1: To identify classes of functional independence and change in class membership over time in aging adult survivors of pediatric bone sarcomas.

Hypothesis 1a: Latent class analysis will identify three classes of functional independence (i.e., independent, moderately independent, and non-independent) among bone sarcoma survivors, similar to those found among brain tumor survivors in SJLIFE and CCSS cohorts.

Hypothesis 1b: Most survivors will remain in the same class or will move to a less functionally independent class over time as they age.

Aim 2: To examine tumor diagnosis, treatment exposures, and late health effects associated with functional independence and change in independence over time.

Hypothesis 2: A history of more intensive chemotherapy regimens, amputation, and the development of chronic health conditions will be associated with failure to attain full independence at baseline, and with incomplete/progressively reduced independence over time.

Aim 3: To examine the association between functional independence and social isolation, financial hardship, activities of daily living, and frailty status in survivors of pediatric bone sarcomas.

Hypothesis 3: Incomplete and progressively reduced independence will be associated with greater risk of social isolation, greater financial hardship, poor performance on activities of daily living, pre-frail/frail status, and health-related quality of life impairment.

Exploratory aim: To examine associations between the type of local control surgery (amputation, limb salvage, or rotationplasty) and functional independence in a subgroup of patients from the expansion cohort. If sufficiently powered, we will evaluate change in functional independence over time in this group as well.

Population

The study population will include adult survivors (aged ≥ 25 years at the time of their baseline survey, given the time required for achievement of adult milestones) in the

entire CCSS cohort with a primary diagnosis of bone sarcoma (either Ewing sarcoma or osteosarcoma) who self-completed the original or expansion baseline surveys and at least one of FU4, FU5, and/or FU7.

Primary outcomes

Functional independence (Original [baseline], Expansion [baseline], FU4, FU5)

Classes of functional and social independence will be identified based on the following indicators:

- 1) Independent living
 - Yes – Own/Rent [Original A9; Expansion A9] or Live with spouse, partner or alone [FU4 M1; FU5 M1; FU7 A9]
 - No – Live with parents or relatives [Original A9; Expansion A9; FU4 M1; FU5 M1; FU7 A9]
- 2) Marital Status [Original L1-L2; Expansion M2-M3; FU4 M2; FU5 M2; FU7 A10]
 - Yes – Married, living as married, widowed, divorced, separated
 - No – Single, never married
- 3) Impairment/health problems preventing work/school [Original N12; Expansion O18; FU4 N24; FU5 N27; FU7 M27]
 - Yes vs. no
- 4) Assistance with personal care needs [Baseline N10; Expansion O16; FU4 N22; F5 N25; FU7 M25]
 - Yes vs. no
- 5) Assistance with routine needs [Baseline N11; Expansion O17; FU4 N23; FU5 N26; FU7 M26]
 - Yes vs. no
- 6) Current driver's license [Baseline N13; Expansion O19; FU4 N25; FU5 N28; FU7 M28]
 - Yes vs. no

Functional independence will be assessed at baseline (i.e., the earliest available assessment for each participant) and follow-up (i.e., the most recent available assessment for each participant) between FU2 and FU7.

We plan to conduct a sensitivity analysis to assess functional independence with and without marital status as an indicator to see if the latent classes are affected and then determine whether marital status is a meaningful contributor to functional independence or would be better replaced by long-term partnership or removed entirely.

In another sensitivity analysis, we will use employment instead of impairment/health problems preventing work/school. However, questions will be different in the original baseline survey compared to the other surveys.

- Yes – Ever had a job and worked in the past 12 months [Baseline O5-O6]; working full time, working part time, caring for home or family, student [Expansion S1-S2; FU4 A4; FU5 A5; FU7 A7]
- No – Did not work in the past 12 months [Baseline O6]; not currently working, unemployed and looking for work, unable to work, retired [Expansion S1-S2; FU4 A4; FU5 A5; FU7 A7]

Secondary outcomes

Social isolation (FU7)

Social isolation will be assessed through the Patient-Reported Outcomes Measurement Information System (PROMIS) Social isolation [FU7 L20].^{20, 21} This is a four-item scale that assesses perceptions of being avoided, excluded, detached, disconnected from, or unknown by, others. The item bank does not use a time frame (e.g. over the past seven days) when assessing social isolation. Age-standardized T-scores (M=50, SD=10) will be used, with higher scores indicating more problems. High social isolation will be defined as a T-score>60.

Frailty (FU7, FU8 long, and FU8 short frailty)

Frailty will be assessed using a modified Fried frailty criteria²² previously defined and applied in the CCSS cohort.^{16, 23} These measures include: **1) low lean muscle mass**, defined as body mass index (BMI) < 18.5 kg/m² [FU7 A1-A2; FU8 A1-A2; FU8 short frailty A1-A2] or unintentional weight loss of ≥10 pounds in the past year [FU7 A3; FU8 A3; FU8 short frailty A3]; **2) exhaustion**, defined as SF-36 vitality subscale score ≤ 40; **3) low energy expenditure**, defined as < 270 Kcal/week for females and <383 kcal/week for males based on responses to duration of low, moderate and vigorous physical activity [FU7 M16-M24; FU8 B5-B13; FU8 short B5-B13]; **4) slowness**, defined as limitations in walking uphill/upstairs, or limitation in walking one block in the past 2 years [FU7 M29c and M29f; FU8 B14a; FU8 short frailty B14a]; and **5) weakness**, defined as having been told to have or have had weakness or inability to move arms by a health care professional [FU7 J11; FU8 B2; FU8 short B2]. Consistent with previous analyses in CCSS,^{16, 23} the frailty phenotype will be defined as:

- 1) non-frail: <2 components of frailty
- 2) pre-frail: 2 components of frailty
- 3) frail: ≥3 components of frailty

Activities of daily living (FU8 long and FU8 short frailty)

Activities of daily living will be assessed through the Katz Index of Activities of Daily Living (ADL)^{24, 25} and the Lawton Instrumental Activities of Daily Living (IADL) Scale.²⁶

Basic ADLs will be assessed through the Katz index of ADL [FU8 long J1; FU8 short frailty E1]. It assesses an individual's ability to perform 6 basic ADLs: bathing and personal hygiene, dressing, toileting, transferring (such as moving from bed to chair), continence (maintaining control of bowel and bladder function), and feeding. The Katz Index assigns a score of either 1 or 0 to each of the six ADLs, indicating whether the person can perform the activity independently (score of 1) or requires assistance (score of 0). The total score ranging from 0 (non-independent) to 6 (fully independent) will be categorized^{27, 28} as:

- disability: score ≤ 2
- relative dependency: score 3-5
- full function: score of 6

Complex ADLs will be assessed through the Lawton Instrumental Activities of Daily Living Scale (IADLs) [FU8 long J2; FU8 short frailty E2]. It assesses more complex activities across 8 domains of function: ability to use telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medication, and ability to handle finances. Responses are scored according to their highest level of functioning in each category (score 0 or 1). The total summary score ranging from 0 (low function, dependent) to 8 (high function, independent) will be used in the analyses.

Health-related quality of life (FU5, FU6 long, and FU7)

Health-related quality of life will be assessed through the Medical Outcomes Survey Short Form-36 (SF-36)²⁹ [FU5 O1-P2; FU6 long E1-F2; FU7 N1-O3]. It includes eight domains: physical function, role limitations due to physical health problems, bodily pain, general health, vitality, social function, role limitations due to physical health problems, and mental health. Age-standardized T-scores will be obtained based on normative data, with higher scores indicating better quality of life. In each domain, T-scores <40 will indicate reduced HRQOL.

Financial hardship (FU6 medium)

Financial hardship will be measured using 21 items that map onto three domains: behavioral hardship [C8], material hardship [C6-C7, C9], and psychological hardship [C17-C19], in addition to two discrete items (sent to debt collection and filing for

bankruptcy).³⁰ A binary scoring method will be used for each domain for an affirmative response to any item within that domain. An alternative approach that uses standardized scores, calculated as the sum of affirmative responses in each domain divided by the standard deviation, will also be explored. Of note, the feasibility of the analysis for this outcome will depend on the number of participants who completed this specific questionnaire at FU6.

Covariates

Sociodemographic characteristics [same time points as the baseline functional independence assessment]:

- Age at survey completion
- Sex:
 - Female
 - Male
- Race/ethnicity:
 - Hispanic
 - Non-Hispanic, White
 - Non-Hispanic, Black
 - Other
- Insurance coverage
 - Yes/Canadian citizen
 - No

Cancer diagnosis [MRAF]:

- Age at diagnosis
- Primary diagnosis:
 - Osteosarcoma
 - Ewing sarcoma
- Tumor location
 - Upper extremity
 - Lower Extremity
 - Pelvis
 - Axial (head, trunk, spine)
- Metastatic disease upon presentation (yes/no)

Treatment variables [MRAF]:

- Surgery type
 - Amputation
 - Rotationplasty (expansion only, for exploratory aim)

- Limb salvage
- Chemotherapy
 - Anthracycline (yes vs. no)
 - Doxorubicin equivalent dose
 - Alkylating agents (yes vs. no)
 - Cyclophosphamide equivalent dose
 - Vinca alkaloid (yes vs. no)
 - Methotrexate (yes vs. no)
 - Etoposide (yes vs. no)
 - Platinum agents (yes vs. no)
- Radiation exposure
 - Any radiation (yes vs. no)
 - Highest total cumulative dose and field
 - All radiation fields with dose

Late chronic health conditions:

- Classified and graded in severity based on the NCI Common Terminology Criteria for Adverse Event (CTCAE) grading system.^{31, 32} Conditions with different onset times will be used depending on the role of these variables in models (see 'Statistical analyses' section).
 - Any condition
 - grade 2-4
 - grade 3-4
 - >1 grade 3-4
 - If feasible, by organ system: musculoskeletal, endocrine, cardiac, pulmonary, neurological, hearing, vision, renal, gastrointestinal (grade 2-4; will narrow to grade 3-4 as necessary)

Pain:

- Dichotomized variable yes/no; yes if any one of the following is met:
 - Headaches (migraines, severe headaches) still present
 - Moderate to very severe bodily pain
 - Current use of opioid and/or non-opioid analgesics, as previously defined in CCSS^{33, 34}
- In each model that includes pain as a covariate, pain aspects reported on or prior to the outcome assessment will be used. For example, pain before FU7 will be used for the social isolation model, and pain before FU8 will be used for frailty.

Statistical analysis

Frequency distributions will be generated to categorize relevant outcome variables, predictors, and covariates according to *a priori* and/or reasonable groupings.

Descriptive statistics including means, standard deviation, medians, ranges, frequencies, and percentages will be calculated for all outcomes, predictors, and covariates. An attempt to establish temporal relationships between the study variables will be made by assessing the primary outcome (i.e., functional independence) at baseline and FU4, FU5, and FU7, whereas the secondary outcomes (i.e., social isolation, frailty, financial hardship, and activities of daily living) will be evaluated at FU6, FU7, and FU8. We will assess secondary variables in relation to baseline functional independence status and will attempt to evaluate trajectories over time if data is adequate.

Aim 1. Latent class analysis using the six indicators of functional independence will be used to identify classes of functional independence at baseline or at the earliest available assessment for each participant. Several analyses with brain tumor survivors from SJLIFE¹⁷ and CCSS^{18, 19} demonstrated three classes of functional independence (i.e., non-independent, moderately independent, independent). Consistent with these past studies, models with one to six classes will be fitted to data and multiple indices including adjusted Bayesian information criterion, entropy and clinical meaning will be examined to select the optimal number of classes (Table 2; see also Table 3). A minimum sample size of 10% in the smallest class will also be required to be able to use subsequent multivariable models.

Another latent class analysis using the six indicators of functional independence will be repeated at follow-up, using the most recent available assessment for each participant to obtain the longest interval of follow-up (Table 2 and Table 4).

Based on the classes identified at baseline and follow-up, different trajectories reflecting changes over time will be defined (Table 5). For example, if the three classes from previous analyses are replicated, the following trajectories will be defined:

- 1) stable independence
 - independent at both time points
- 2) stable non-independence:
 - non-independent at both time points
- 3) improved independence
 - moving from non-independent to moderately independent
 - moving from moderately independent to independent
- 4) worsened independence:
 - moving from independent to moderately independent or non-independent
 - moving from moderately independent to non-independent

It is possible that the classes of functional independence obtained with a data-driven approach do not overlap qualitatively between baseline and follow-up. In this case, we

will build latent classes based on baseline and follow-up together as an alternative approach.

A preliminary data request indicated that N=1396 bone tumor survivors aged ≥ 25 years who completed baseline survey, and n=851 (61%) are evaluable on at least two time points.

Aim 2. Binomial or multinomial logistic regressions will examine the associations between cancer diagnosis, treatment exposures, and late chronic health conditions (predictors, in separate models) and the classes of functional independence at baseline (outcomes; binary or categorical). Specifically, chronic conditions with onset on or prior to the first functional independence assessment will be used. All models will be adjusted for sex, race/ethnicity, age at functional independence baseline assessment and age at diagnosis (Table 6).

Multinomial logistic regressions will also examine the associations between cancer diagnosis, treatment exposures, and late chronic health conditions (predictors, in separate models) and the trajectories of functional independence between baseline and follow-up (outcomes; categorical). Specifically, chronic conditions with onset on or prior to the last functional independence assessment will be used. All models will be adjusted for sex, race/ethnicity, age at functional independence baseline assessment and age at diagnosis (Table 7).

Aim 3. A series of multivariable models will be used to examine the associations between the classes of functional independence at baseline (predictors) and subsequent social isolation, financial hardship, ADLs, health-related quality of life and frailty (outcomes). Specifically, logistic regression models will predict the PROMIS social isolation, health-related quality of life impairment, and financial hardship (binary outcomes; Table 8, 12, and 13), multinomial logistic regression models will predict the scores of the Katz's ADLs scale and frailty status (categorical/ordinal outcome; Table 9 and 11), and linear regression models will predict the score of the Lawton's IADLs scale (continuous outcomes; 10). All models will be adjusted for sex, race/ethnicity, pain, and any grade 3-4 chronic health condition with onset on or prior to the model-specific outcome. We will also explore the variability in time between functional independence baseline assessment (T1), T2, and the secondary outcomes to better inform appropriate adjustment for age.

Another series of multivariable models will be used to examine the associations between the trajectories of functional independence between baseline and follow-up (predictors) and subsequent social isolation, financial hardship, ADLs and frailty (outcomes) (Tables 8-13). All models will be adjusted for sex, race/ethnicity, pain, and any grade 3-4 chronic health condition with onset on or prior to the model-specific outcome. We also plan to adjust for age at baseline assessment and age at latest

follow-up assessment with options to modify based on variability found between T1, T2, and secondary outcomes, as above.

A preliminary data request indicated that, out of n=851 survivors aged ≥ 25 years and evaluable for functional independence at least two time points, 60% to 70% have secondary outcome data.

Exploratory aim. Detailed information about contemporary surgical procedures that could impact functional independence, including rotationplasty, is available in the CCSS only for the expansion cohort. We plan to review previously curated data sets³⁵ that code surgical procedures to ensure appropriate surgical classification and will review these codes over time to account for any revisions. We propose to examine surgical procedures associated with functional independence and change in independence over time in this subgroup of survivors utilizing the same analysis plan and independent covariables as used for the primary aims (Table 14 and 15).

Table 1. Sample characteristics

	Survivors (N =)
	Mean (SD)
Age at diagnosis, years	
Age at follow-up, years	
	N (%)
Sex	
Female	
Male	
Race/ethnicity	
Hispanic	
Non-Hispanic White	
Non-Hispanic Black	
Other	
Insurance coverage	
Yes/Canadian citizen	
No	
Cancer diagnosis	
Osteosarcoma	
Ewing sarcoma	
Tumor location	
Upper extremity	
Lower extremity	
Pelvis	
Axial (head, trunk, spine)	
Metastatic disease at presentation	
Yes	
No	
Treatment exposures	
Chemotherapy	
Anthracycline	
Doxorubicin equivalent dose	
Alkylating agents	
Cyclophosphamide equivalent dose	
Vinca alkaloid	
Methotrexate	
Etoposide	
Platinum agents	
Radiation Therapy	
Yes	
No	
Max Cumulative Radiation dose	
RT Field/Dose 1	
RT Field/Dose 2	
RT Field/Dose 3	

	Survivors (N =)
Surgical procedures	
Limb salvage	
Rotationplasty	
Amputation	
Chronic health conditions	
Any grade 2-4	
Any grade 3-4	
>1 grade 3-4	
Grade 2-4 musculoskeletal	
Grade 2-4 endocrine	
Grade 2-4 cardiac	
Grade 2-4 pulmonary	
Grade 2-4 neurologic	
Grade 2-4 vision	
Grade 2-4 hearing	
Grade 2-4 renal	
Grade 2-4 gastrointestinal	
Employment	
Full time	
Part time	
Unemployed	
Marital status	
Single, never married	
History of marriage/partnership	
Independent living	
Yes	
No	
Driver license	
Yes	
No	
Assistance with routine needs	
Yes	
No	
Assistance with personal care needs	
Yes	
No	
Pain	
Yes	
No	
Health-related quality of life ^b	
Physical function	
Physical role	
Bodily pain	
General health	

	Survivors (N =)
Vitality	
Social function	
Role emotional	
Mental health	

Abbreviations: SD, standard deviation.

^a Impairment: T-score ≥ 63 .

^b Impairment: T-score < 40 .

Table 2. Model fit indices from the latent class analysis at baseline and follow-up

Timepoint	Model	Log-Likelihood	G ²	AIC	BIC	Consistent AIC	Adjusted BIC	Entropy
Baseline	1-class							
	2-class							
	3-class							
	4-class							
	5-class							
Follow-up	1-class							
	2-class							
	3-class							
	4-class							
	5-class							

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion.

Table 3. Indicators of functional independence by latent classes at baseline

	Classes of functional independence*		
	Independent (n =)	Moderately independent (n =)	Non- independent (n =)
	n (%)	n (%)	n (%)
Unemployed			
Unmarried			
Non-independent living			
No driver's license			
Assistance with routine needs			
Assistance with personal care needs			

* The number of latent classes and their labels will depend on the results of the latent class analysis.

Table 4. Indicators of functional independence by latent classes at follow-up

	Classes of functional independence*		
	Independent (n =)	Moderately independent (n =)	Non- independent (n =)
	n (%)	n (%)	n (%)
Unemployed			
Unmarried			
Non-independent living			
No driver's license			
Assistance with routine needs			
Assistance with personal care needs			

* The number of latent classes and their labels will depend on the results of the latent class analysis.

Table 5. Trajectories of functional independence between baseline and follow-up

	Trajectories of functional independence*			
	Stable independence (n = , %)	Stable non-independence (n = , %)	Improved independence (n = , %)	Worsening independence (n = , %)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age at diagnosis, years				
Age at follow-up, years				
	n (%)	n (%)	n (%)	n (%)
Sex				
Female				
Male				
Race/ethnicity				
Hispanic				
Non-Hispanic White				
Non-Hispanic Black				
Other				
Cancer diagnosis				
Osteosarcoma				
Ewing sarcoma				
Location				
Upper extremity				
Lower extremity				
Pelvis				
Axial (head, trunk, spine)				
Metastatic disease at presentation				
Yes				
No				
Treatment exposures				
Chemotherapy				
Anthracycline				
Doxorubicin equivalent dose				
Alkylating agents				
Cyclophosphamide equivalent dose				
Vinca alkaloid				
Methotrexate				
Etoposide				

	Trajectories of functional independence*			
	Stable independence (n = , %)	Stable non-independence (n = , %)	Improved independence (n = , %)	Worsening independence (n = , %)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Platinum agents				
Radiation Therapy				
Yes				
No				
Max cumulative radiation dose/site				

Abbreviations: SD, standard deviation.

* The number of trajectories of functional independence and their labels will depend on the results of the latent class analysis at baseline and follow-up.

Table 6. Associations between cancer diagnosis, treatment exposures, surgical procedures and late chronic health conditions and the classes of functional independence at baseline

	Classes of functional independence*					
	Independent		Moderately independent		Non-independent	
	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
Cancer diagnosis						
Osteosarcoma		Ref.		Ref.		Ref.
Ewing sarcoma						
Treatment exposures						
Chemotherapy						
Anthracycline						
Doxorubicin equivalent dose						
Alkylating agents						
Cyclophosphamide equivalent dose						
Vinca alkaloid						
Methotrexate						
Etoposide						
Platinum agents						
Radiation Therapy						
Yes						
No						
Max Cumulative radiation dose/site						
Chronic health conditions (grade 0-1 vs. 2-4)						
Musculoskeletal						
Endocrine						
Cardiac						
Pulmonary						
Neurological						
Hearing						
Vision						
Renal						
Gastrointestinal						

Multivariable models adjusted for sex, race/ethnicity, age at the baseline functional independence assessment, and age at diagnosis. Cancer diagnosis, treatment exposure, surgical procedures and late chronic health conditions assessed in separate models.

Abbreviations: CI, confidence interval; RR, relative risk.

* The number of latent classes and their labels will depend on the results of the latent class analysis. Class 1 represents the “healthy” independent class that will be used as reference group.

Table 7. Associations between cancer diagnosis, treatment exposures, surgical procedures and late chronic health conditions (predictors) and trajectories of functional independence between baseline and follow-up

	Trajectories of functional independence*			
	Stable independence (n = , %)	Improved independence (n = , %)	Worsening independence (n = , %)	Stable non-independence (n = , %)
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Cancer diagnosis				
Osteosarcoma	Ref.	Ref.	Ref.	Ref.
Ewing sarcoma				
Treatment exposures				
Chemotherapy				
Anthracycline				
Doxorubicin equivalent dose				
Alkylating agents				
Cyclophosphamide equivalent dose				
Vinca alkaloid				
Methotrexate				
Etoposide				
Platinum agents				
Radiation Therapy				
Yes				
No				
Cumulative radiation dose/site				
Chronic health conditions (grade 0-1 vs. 2-4)				
Musculoskeletal				
Endocrine				
Cardiac				
Pulmonary				
Neurological				
Hearing				
Vision				
Renal				
Gastrointestinal				

Multivariable models adjusted for sex, race/ethnicity, age at the baseline functional independence assessment, and age at diagnosis. Cancer diagnosis, treatment exposure, surgical procedures and late chronic health conditions assessed in separate models.

* The number of trajectories of functional independence and their labels will depend on the results of the latent class analysis at baseline and follow-up.

Abbreviations: SD, standard deviation.

Table 8. Association between classes of functional independence at baseline and trajectories of independence over time and social isolation impairment

Functional independence	Social isolation impairment	
	n (%)	RR (95% CI)
Classes at baseline		
Independent		Ref.
Moderately independent		
Non-independent		
Trajectories over time		
Stable independence		Ref.
Improved independence		
Stable non-independence		
Worsening independence		

Multivariable models adjusted for sex, race/ethnicity, age at the baseline functional independence assessment, pain, and any grade 3-4 chronic condition. Social isolation impairment defined as T-score >60.

Abbreviations: CI, confidence interval; RR, relative risk.

* The number of classes and trajectories and their labels will depend on the results of the latent class analyses.

Table 9. Associations between classes of functional independence at baseline and trajectories of independence over time and basic activities of daily living

	Full function		Relative dependency		Disability	
Functional independence*	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
Classes at baseline						
Independence		Ref.		Ref.		Ref.
Moderately independent		Ref.				
Non-independent		Ref.				
Trajectories over time						
Stable independence		Ref.		Ref.		Ref.
Improved independence		Ref.				
Stable non-independence		Ref.				
Worsening independence		Ref.				

Multivariable models adjusted for sex, race/ethnicity, age at the baseline functional independence assessment, pain, and any grade 3-4 chronic condition.

Abbreviations: CI, confidence interval; RR, relative risk.

* The number of classes and trajectories and their labels will depend on the results of the latent class analyses.

Table 10. Associations between classes of functional independence at baseline and trajectories of functional independence over time and instrumental activities of daily living

Functional independence*	Instrumental activities of daily living	
	n (%)	β (SE)
Classes of independence		
Independence		Ref.
Moderately independent		
Non-independent		
Trajectories over time		
Stable independence		Ref.
Improved independence		
Worsening independence		
Stable non-independence		

Multivariable models adjusted for sex, race/ethnicity, age at the baseline functional independence assessment, pain, and any grade 3-4 chronic condition.

Abbreviations: SE, standard error.

* The number of classes and trajectories and their labels will depend on the results of the latent class analyses.

Table 11. Associations between classes of functional independence at baseline and trajectories of functional independence over time and frailty status

	Non-frail		Pre-frail		Frail	
Functional independence*	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
Classes at baseline						
Independence		Ref.		Ref.		Ref.
Moderately independent		Ref.				
Non-independent		Ref.				
Trajectories over time						
Stable independence		Ref.		Ref.		Ref.
Improved independence		Ref.				
Worsening independence		Ref.				
Stable non-independence		Ref.				

Multivariable models adjusted for sex, race/ethnicity, age at the baseline functional independence assessment, pain, and any grade 3-4 chronic condition.

Abbreviations: CI, confidence interval; RR, relative risk.

* The number of classes and trajectories and their labels will depend on the results of the latent class analyses.

Table 12. Associations between classes of functional independence at baseline and trajectories of functional independence over time and health-related quality of life

	Physical function		Role physical		Bodily pain		General health		Vitality		Social function		Role emotional		Mental health	
Functional independence*	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
Classes at baseline																
Independence		Ref.		Ref.		Ref.		Ref.								
Moderately independent		Ref.														
Non-independent		Ref.														
Trajectories over time																
Stable independence		Ref.		Ref.		Ref.		Ref.								
Improved independence		Ref.														
Worsening independence		Ref.														
Stable non-independence		Ref.														

Multivariable models adjusted for sex, race/ethnicity, age at the baseline functional independence assessment, pain, and any grade 3-4 chronic condition.

Abbreviations: CI, confidence interval; RR, relative risk.

* The number of classes and trajectories and their labels will depend on the results of the latent class analyses.

Table 13. Association between classes of functional independence at baseline and trajectories of independence over time and financial hardship

	Financial hardship					
	Behavioral hardship		Material hardship		Psychological hardship	
Functional independence	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
Classes at baseline						
Independent		Ref.		Ref.		Ref.
Moderately independent						
Non-independent						
Trajectories over time						
Stable independence		Ref.		Ref.		Ref.
Improved independence						
Stable non-independence						
Worsening independence						

Multivariable models adjusted for sex, race/ethnicity, age at the baseline functional independence assessment, pain, and any grade 3-4 chronic condition.

Abbreviations: CI, confidence interval; RR, relative risk.

* The number of classes and trajectories and their labels will depend on the results of the latent class analyses.

Table 14. Distribution of surgical procedures and the classes of functional independence at baseline

	Classes of functional independence*		
	Independent	Moderately independent	Non-independent
	n (%)	n (%)	n (%)
Surgical procedures			
Limb salvage			
Rotationplasty			
Amputation			

* The number of latent classes and their labels will depend on the results of the latent class analysis. Class 1 represents the “healthy” independent class that will be used as reference group.

Table 15. Distribution of surgical procedures and trajectories of functional independence between baseline and follow-up

	Trajectories of functional independence*			
	Stable independence (n = , %)	Stable non-independence (n = , %)	Improved independence (n = , %)	Worsening independence (n = , %)
	n (%)	n (%)	n (%)	n (%)
Surgical procedures				
Limb salvage				
Rotationplasty				
Amputation				

Abbreviations: SD, standard deviation.

* The number of trajectories of functional independence and their labels will depend on the results of the latent class analysis at baseline and follow-up.

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