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Unemployment in patients with histiocytic neoplasms is frequent and associated with clinical and treatment characteristics

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List of abbreviations:

HN: Histiocytic neoplasms
OR: Odds ratio
CI: Confidence interval
LCH: Langerhans cell histiocytosis
ECD: Erdheim-Chester disease
RDD: Rosai-Dorfman disease
JXG/AXG: Juvenile/adult xanthogranuloma
PRO: Patient-reported outcome
FACT-G: Functional assessment of cancer therapy, general
BFI: Brief Fatigue Inventory
BPI: Brief Pain Inventory
HADS: Hospital anxiety and depression scale
FACT-Cog: Functional assessment of cancer therapy, cognition
QoL: Health-related quality of life

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Histiocytic neoplasms (HN) are comprised of Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), Rosai-Dorfman disease (RDD), and juvenile/adult xanthogranuloma (JXG/AXG). The emergence and regulatory approval of targeted therapies[1-4], and for many patients chronic disease suppression—rather than cure—with these agents, prompt the need to understand how patients with HN maintain function and quality of life (QoL) amid ongoing disease symptoms, treatment effects, and psychosocial challenges. Cancer broadly impacts employment with approximately 1 in 3 cancer survivors unemployed; additionally, patients with cancer are ~40% more likely to be unemployed than healthy controls.[5] We have reported that HN patients experience higher rates of anxiety and depression compared with patients with other cancers.[6] We have also demonstrated diverse symptomatology, notably fatigue and pain, and diminished QoL in patients with ECD.[7-9] Disease rarity and heterogeneity in HN contribute to diagnostic delays, which are associated with unfavorable psychosocial outcomes.[6] Financial strain, employment status, depression, and anxiety are well-recognized consequences for cancer survivors.[10] However, the interplay of these factors in relation to employment is unknown in HN. Herein, we estimated unemployment rates and identified factors associated with unemployment among patients with HN. We hypothesized that unemployment would be common in HN and associated with symptomatology and other salient challenges inherent to living with a rare cancer.

This is an institutional review board-approved, registry-based study conducted at Memorial Sloan Kettering Cancer Center (MSKCC; NCT03329274), enrolling participants within and outside MSKCC. Participants providing informed consent enrolled from 2018-2025 and completed patient-reported outcomes (PROs) at the time of enrollment, and two other timepoints. PROs included employment status categorized: full-time, part-time, unemployed, or retired. The current study included participants if they reported full-time, part-time, or unemployed status at enrollment.

Demographic and clinical variables including HN type, time from symptom onset to diagnosis (undiagnosed duration), time from diagnosis to enrollment (diagnosed duration) sites of disease, comorbidities, and treatments were ascertained as previously described.[6,8,9] HN treatment status at enrollment was categorized as conventional (chemotherapy or immunosuppression), targeted (BRAF or MEK inhibitor), or no current treatment. In addition to employment, eight other PROs previously described[6,9] were ascertained: financial burden and worry; Functional Assessment of Cancer Therapy, General (FACT-G); Functional Assessment of Cancer Therapy, Cognition (FACT-Cog); an HN symptom inventory, initially content-validated in ECD (ECD-SS); Brief Fatigue Inventory (BFI); Brief Pain Inventory (BPI); Hospital Anxiety and Depression Scale (HADS); and Supportive Care Needs Survey (SCNS).

Our primary objective was to estimate unemployment rates and identify risk factors associated with unemployment at enrollment, comparing participants who reported unemployment with those reporting employment (full-time/part-time). SCNS items were dichotomized as met (no/low need) or unmet (moderate/high need) need. If any item within a factor was unmet, the factor was classified as unmet; the number of unmet items was also summed. Univariable associations with unemployment were modeled with logistic regression to estimate odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Potential clinical confounders were selected a priori for adjustment in multivariable models and included: age, undiagnosed illness duration, fatigue, pain, brain involvement, number of sites of disease, and household income. In a post-hoc analysis, we formally tested whether the impact of FACT-Cog subscales on unemployment varied by brain involvement. All tests were 2-sided with statistical significance <0.05. Analyses were performed in SAS v9.4 (SAS Institute, Cary, NC).

Two hundred enrolled patients with HN who were eligible for employment had a median age at enrollment of 51.1 years (range:21.6-72.2) (Table 1). HN subtypes included: 99 (49.5%) with ECD, 42 (21.0%) with LCH, 26 (13.0%) with RDD, and 14 (5.5%) with AXG. The median diagnosed illness duration was 4.1 years (range:0.2-48.1).

Fifty-one patients (25.5%) reported being unemployed at enrollment (Table 1). The unemployment rate was 24.3% at timepoint 1 (IQR:6.0-7.8 months from enrollment) and 30.9% at timepoint 2 (IQR:12.8-16.0 months from enrollment, max:31.7 months from enrollment). Of 140 patients reporting employment status at enrollment and timepoint 1, 120 patients (85.7%) remained in the same category (Table 2, Supplemental Figure 1A), including 32 patients (22.9%) who were unemployed at both timepoints. Similar trends were observed at timepoint 2 (Table 2, Supplemental Figure 1B).

In univariable models, risk factors for unemployment included being female, ECD, longer undiagnosed HN duration, brain parenchymal involvement, and targeted treatment. Nineteen percent of patients not on treatment at enrollment reported unemployment compared to 27% undergoing conventional and 35% on targeted treatment. Unemployment was also associated with lower household income, worse general and cognitive QoL, greater symptom severity including pain and fatigue, greater unmet supportive care needs, depression, and financial burden (Table 3).

In multivariable models, risk factors for unemployment included longer undiagnosed HN duration (OR:1.13, 95%CI:1.03-1.25, p=0.01), brain parenchymal involvement (OR:3.60, 95%CI:1.36-9.54, p=0.01), targeted treatment compared with no treatment (OR:3.78, 95%CI:1.38-10.36, p=0.0096), household annual income $0-$75,000 (OR:2.30, 95%CI:1.00-5.30, p=0.0497), worse functional well-being (OR:1.15, 95%CI:1.05-1.25, p=0.002), moderate/severe depression (OR:10.96, 95%CI:2.84-42.24, p=0.0005) and greater impact of perceived cognitive impairments on QoL (OR:1.19, 95%CI:1.05-1.34, p=0.007). The impact of FACT-Cog subscales on unemployment was not heterogeneous by brain involvement.

This is the first systematic study of employment in HN. In 200 patients, nearly 1 in 4 patients with HN reported unemployment at enrollment, a rate increasing to nearly 1 in 3 over time. Comparably, a meta-analysis of >20,000 cancer survivors reported an unemployment rate of 33.8% across a range of 9 months to 15 years post-diagnosis compared to 15% of healthy

controls.[5] In 904 employed patients with myeloproliferative neoplasms, a first change in employment status occurred approximately 2 years after diagnosis with 30.2% leaving a job.[11] Our findings suggest that unemployment rates among patients with HN, with a median of 5 years since diagnosis, are broadly comparable to other cancers, including hematological. However, most patients with HN have not undergone extensive surgery, radiation, intensive multi-agent chemotherapy, or transplantation, interventions common for other cancers. In our cohort, where chemotherapy administration was rare, and HN regimens are generally single-agent and less intensive than those for solid tumors or leukemias and lymphomas, unemployment rates were higher than may be expected considering the absence of these treatment-related factors. Rather, our results suggest that targeted therapy, often chronic in HN, may itself pose challenges for employment.

After confounder adjustment, seven variables emerged as independently associated with unemployment: longer diagnostic delay, brain involvement, targeted therapy, lower functional well-being, lower household income, moderate/severe depression and greater impact of perceived cognitive impairments on QoL. These findings mirror observations from the broader cancer literature where cognitive difficulties and sadness were predictors of unemployment.[12] For HN, the constellation of reduced functional well-being and moderate/severe depression represents a common symptomatology cluster;[6,8,9] our current findings extend their impact to employment outcomes. The association between neurologic involvement of HN and unemployment is consistent with clinical experience that patients with brain parenchymal HN often experience functional impairments and limited treatment responses.[13] However, reverse association of more severe disease leading to both unemployment and treatment cannot be excluded. The association between unemployment and longer undiagnosed illness, frustratingly common in HN, brings awareness to additional harmful consequences of delayed diagnosis.

This study raises an important question of how to mitigate the impact of HN upon employment viability. Educating employers about HN manifestations may allow for

accommodations to maintain employment; even perceived employer accommodations for symptoms, side effects, and follow-up visits for cancer and cancer treatment are strong predictors of return to work, as are flexible working conditions, counseling, and job search assistance.[14] Additionally, recognizing that fatigue and pain, often elusive symptoms, are cancer-related in HN may contribute to employer accommodations. While a Cochrane review demonstrated that psycho-educational interventions alone are unlikely to improve return-to-work rates, multidisciplinary and physical interventions may have greater success, though most studies were in breast cancer.[15] For patients with HN, targeted interventions such as management of depression, optimal therapies for neurologic involvement, and reduction in diagnostic delay may improve the likelihood of sustained employment.

Our study has some limitations. As a registry-based, cross-sectional cohort, some heterogeneity is inherent by design. While there was a mixed referral base, there was a substantial representation from MSKCC. Registry participants may be more engaged, potentially inflating unemployment rates, though estimates were comparable to those reported in the broader cancer survivorship literature. Employment status was self-reported, though this is conventional in published literature. High rates of missing employment status post-enrollment limited our ability to draw longitudinal conclusions. Lack of changes in known employment distribution from enrollment to timepoint 2 precluded analyses investigating associations with change in employment status over time. Nonetheless, the finding that most patients unemployed at enrollment remained unemployed at timepoint 2 suggests that the enrollment associations likely persist over time.

Employment is a vital component of functioning and well-being in people with active cancer and in cancer survivorship, including those with HN. We demonstrated that unemployment is both common and persistent in HN and is associated with an array of factors, some of which are modifiable. These findings present intervention opportunities through symptom management, earlier diagnosis, improved treatment of neurologic disease, and

workplace accommodations that could help preserve employment and by extension QoL for patients with HN.

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Table 1. Cohort characteristics.

Variable	Category	N	%	Median	Range
Age at histiocytosis diagnosis	Continuous, years	199	99.5	46.4	0.4-69.8
Age at registry enrollment	Continuous, years	200	100	51.1	21.6-72.2
Histiocytosis diagnosis	ECD	99	49.5		
	LCH	42	21.0		
	RDD	26	13.0		
	AXG	11	5.5		
	HS	3	1.5		
	Mixed ECD/LCH	13	6.5		
	Mixed ECD/RDD	4	2.0		
	Other	2	1.0		
Histiocytosis diagnosis	ECD, mixed ECD/LCH, mixed ECD/RDD	116	58.0		
	LCH	42	21.0		
	RDD	26	13.0		
	AXG, HS, Other	16	8.0		
Registry enrollment	MSKCC	164	82.0		
	Outside MSKCC	36	18.0		
Sex	Male	104	52.0		
	Female	96	48.0		
Length of undiagnosed illness	Continuous, years	199	99.5	0.6	0-21.3
Length of diagnosed illness	Continuous, years	200	99.6	4.1	0.2-48.1
Sites of disease	Bone	146	73.0		
	Neurologic	104	52.0		
	Brain Parenchyma	80	40.0		
	Cardiovascular	52	26.0		
	Pulmonary	34	17.0		
	Retroperitoneum	57	28.5		
	Abdomen	28	14.0		
	Skin/Subcutaneous	64	32.0		
	Lymph Node	29	14.5		
	Other	35	17.5		
Hypertension	No	126	63.0		
	Yes	74	37.0		
Diabetes	No	164	82.0		
	Yes	36	18.0		
Treatment at enrollment	None	106	53.0		
	Conventional	15	7.5		
	Targeted	78	39.0		
	Unknown	1	0.5		
Household annual income	$0-$25,000	17	8.5		
	$25,000-$50,000	15	7.5		
	$50,000-$75,000	20	10.0		
	$75,000-$100,000	20	10.0		
	$100,000+	89	44.5		
	Unknown or prefer not to answer	39	19.5		

Highest education level	Some high school	3	1.5		
	High school	31	15.5		
	Undergraduate	73	36.5		
	Graduate	67	33.5		
	Postgraduate	26	13.0		
Employment at Enrollment	Part-time	31	15.5		
	Full-time	118	59.0		
	Unemployed	51	25.5		
Employment at Timepoint 1 (IQR: 6.0-7.8 months from enrollment)[a]	Part-time	21	15.0		
	Full-time	75	53.6		
	Unemployed	34	24.3		
	Retired	10	7.1		
	Unknown	60			
Employment at Timepoint 2 (IQR: 12.8-16.0 months from enrollment)[a]	Part-time	9	11.1		
	Full-time	37	45.7		
	Unemployed	25	30.9		
	Retired	10	12.4		
	Unknown	119			

[a]Unknowns not included in denominator for proportions.

Table 2. Known Employment Distributions Across Time Trajectories.

Enrollment Employment	**Employment at Timepoint 1[a]**	**N**	**%**
Part-time	Part-time	13	9.3
Part-time	Unemployed	2	1.4
Part-time	Retired	1	0.7
Full-time	Part-time	3	2.1
Full-time	Full-time	75	53.6
Full-time	Retired	5	3.6
Unemployed	Part-time	5	3.6
Unemployed	Unemployed	32	22.9
Unemployed	Retired	4	2.9
Enrollment Employment	**Employment at Timepoint 2[b]**	**N**	**%**
Part-time	Part-time	5	6.2
Part-time	Full-time	1	1.2
Part-time	Unemployed	2	2.5
Full-time	Part-time	3	3.7
Full-time	Full-time	35	43.2
Full-time	Unemployed	2	2.5
Full-time	Retired	4	4.9
Unemployed	Part-time	1	1.2
Unemployed	Full-time	1	1.2
Unemployed	Unemployed	21	25.9
Unemployed	Retired	6	7.4

[a] IQR: 6.0-7.8 months from enrollment.

[b] IQR: 12.8-16.0 months from enrollment

Table 3. Associations with Unemployment Status at Enrollment (versus all full-time or part-time employment). N=200

Variable	Category	N	%	Univariable			Multivariable		
				OR	95% CI	P-value	OR[a]	95% CI[a]	P-value[a]
Age at histiocytosis diagnosis	Continuous, years	199	99.5	1.00	0.97-1.02	0.78	1.01	0.98-1.05	0.40
Age at registry enrollment	Continuous, years	200	100	0.99	0.96-1.02	0.49	1.01	0.97-1.04	0.80
Histiocytosis diagnosis (binary)	Non-ECD	84	42.0	Ref			Ref		
	ECD or Mixed ECD	116	58.0	2.07	1.05-4.10	0.04	1.82	0.66-4.98	0.25
Sex	Male	104	52.0	Ref			Ref		
	Female	96	48.0	2.00	1.05-3.83	0.04	1.98	0.96-4.74	0.13
Length of undiagnosed illness	Continuous, years	199	99.5	1.09	1.01-1.18	0.02	1.13	1.03-1.25	0.01
Length of diagnosed illness	Continuous, years	200	100	1.01	0.98-1.06	0.48	0.95	0.88-1.03	0.24
Sites of disease	Bone	146	73.0	1.41	0.66-3.00	0.38	2.36	0.71-7.80	0.16
	Neurologic	104	52.0	1.41	0.74-2.69	0.30	1.50	0.59-3.83	0.39
	Brain Parenchyma	80	40.0	2.22	1.17-4.25	0.02	3.60	1.36-9.54	0.01
	Cardiovascular	52	26.0	1.40	0.69-2.82	0.35	1.74	0.64-4.74	0.28
	Pulmonary	34	17.0	1.47	0.66-3.28	0.35	1.27	0.44-3.65	0.66
	Retroperitoneum	57	28.5	1.03	0.51-2.08	0.93	0.85	0.33-2.19	0.73
	Abdomen	28	14.0	1.17	0.48-2.85	0.73	1.09	0.33-3.56	0.89
	Skin/Subcutaneous	64	32.0	1.05	0.54-2.07	0.88	0.94	0.35-2.55	0.90
	Lymph Node	29	14.5	0.71	0.27-1.85	0.48	1.33	0.39-4.53	0.65
Multisystemic	No	48	24.0	Ref			Ref		
	Yes	151	75.5	1.04	0.49-2.21	0.91	0.49	0.16-1.52	0.22
Treatment	None	106	53.0	Ref			Ref		
	Conventional	15	7.5	1.56	0.45-5.42	0.48	2.66	0.63-11.24	0.19
	Targeted	78	39.0	2.28	1.16-4.47	0.02	3.78	1.38-10.36	0.0096
Household annual income	≥$75,000	109	54.5	Ref			Ref		
	$0-$75,000	52	26.0	2.73	1.29-5.78	0.009	2.30	1.00-5.30	0.0497
Highest education level	<Undergraduate	34	17.0	Ref			Ref		
	≥Undergraduate	166	83.0	0.66	0.30-1.48	0.32	1.55	0.48-5.07	0.47
Hypertension	No	74	37.0	Ref			Ref		
	Yes	126	63.0	0.81	0.41-1.58	0.53	1.02	0.42-2.45	0.97
Diabetes	No	164	82.0	Ref			Ref		
	Yes	36	18.0	0.97	0.42-2.23	0.94	1.30	0.46-3.71	0.62
FACT-G physical well being[b]	Continuous	199	99.5	0.91	0.87-0.96	0.0002	0.94	0.85-1.05	0.27
FACT-G emotional well being[b]	Continuous	199	99.5	0.99	0.93-1.06	0.71	1.07	0.97-1.18	0.21
FACT-G social well being[b]	Continuous	199	99.5	0.95	0.91-1.00	0.06	0.99	0.92-1.06	0.70
FACT-G functional well being[b]	Continuous	199	99.5	0.87	0.82-0.92	<0.0001	0.87	0.80-0.95	0.002
FACT-G total score[b]	Continuous	199	99.5	0.97	0.95-0.98	0.0002	0.98	0.95-1.01	0.19
BPI severity[c]	Continuous	197	98.5	1.14	1.01-1.28	0.04	1.00	0.84-1.19	1.00
BPI interference[c]	Continuous	197	98.5	1.22	1.09-1.37	0.0004	1.17	0.995-1.37	0.06
BPI total[c]	Continuous	197	98.5	1.22	1.08-1.37	0.002	1.13	0.94-1.35	0.19

BFI severity[d]	Continuous	196	98.0	1.18	1.06-1.31	0.002	1.00	0.86-1.17	0.96
BFI interference[d]	Continuous	197	98.5	1.26	1.13-1.40	<0.0001	1.15	0.996-1.33	0.06
BFI total[d]	Continuous	197	98.5	1.26	1.12-1.40	<0.0001	1.12	0.96-1.30	0.17
ECDSS Top 3 Symptoms Severity[e]	Continuous	189	94.5	1.39	1.16-1.66	0.0004	1.15	0.88-1.50	0.32
ECDSS Top 5 Symptoms Severity[e]	Continuous	189	94.5	1.42	1.17-1.73	0.0004	1.12	0.83-1.51	0.47
Unmet health care service needs	No	114	57.0	Ref			Ref		
	Yes	76	38.0	1.49	0.78-2.84	0.23	0.59	0.23-1.47	0.25
Unmet psychological/emotional needs	No	86	43.0	Ref			Ref		
	Yes	110	55.0	1.74	0.89-3.40	0.11	2.06	0.76-5.56	0.16
Unmet physical and daily health needs	No	98	49.0	Ref			Ref		
	Yes	98	49.0	2.26	1.17-4.37	0.02	1.57	0.53-4.64	0.41
Unmet care and support needs	No	146	73.0	Ref			Ref		
	Yes	47	23.5	2.42	1.20-4.88	0.01	1.29	0.51-3.27	0.59
Unmet sexual needs	No	152	76.0	Ref			Ref		
	Yes	40	20.0	2.16	1.03-4.57	0.04	1.92	0.74-5.04	0.18
Number of unmet needs	Continuous	198	99.0	1.07	1.03-1.11	0.0006	1.04	0.99-1.10	0.14
Unmet Needs	<3	81	40.5	Ref			Ref		
	3+	117	58.5	2.52	1.24-5.11	0.01	1.31	0.48-3.55	0.60
	<5	102	51.0	Ref			Ref		
	5+	96	48.0	2.74	1.41-5.35	0.003	2.07	0.77-5.59	0.15
	<10	140	70.0	Ref			Ref		
	10+	58	29.0	2.34	1.20-4.57	0.01	1.69	0.66-4.28	0.27
Anxiety	Normal/Mild	165	82.5	Ref			Ref		
	Moderate/Severe	35	17.5	1.43	0.65-3.18	0.38	0.67	0.21-2.10	0.49
Depression	Normal/Mild	174	87.0	Ref			Ref		
	Moderate/Severe	26	13.0	9.61	3.85-23.99	<0.0001	10.96	2.84-42.24	0.0005
Financial burden[f]	Continuous	197	98.5	1.30	1.05-1.62	0.02	1.07	0.78-1.48	0.67
FACT-Cog: perceived cognitive impairments[g]	Continuous	200	100	0.98	0.96-1.00	0.12	1.01	0.97-1.05	0.65
FACT-Cog: perceived cognitive impairments QoL[g]	Continuous	199	99.5	0.87	0.82-0.93	<0.0001	0.84	0.75-0.96	0.007
FACT-Cog: comments from others	Continuous	200	100	0.90	0.81-1.01	0.07	0.94	0.80-1.10	0.43
FACT-Cog: perceived cognitive abilities	Continuous	199	99.5	0.97	0.93-1.01	0.09	0.96	0.91-1.02	0.17

[a]Adjusted for age, length of undiagnosed histiocytosis, brain/neurologic involvement, number of sites (multifocal/unifocal), household annual income, BFI total, and BPI total.

[b]A higher FACT-G subscale or total score indicates better well-being.

[c]A higher BPI subscale or total score indicates worse pain.

[d]A higher BFI subscale or total score indicates worse fatigue.

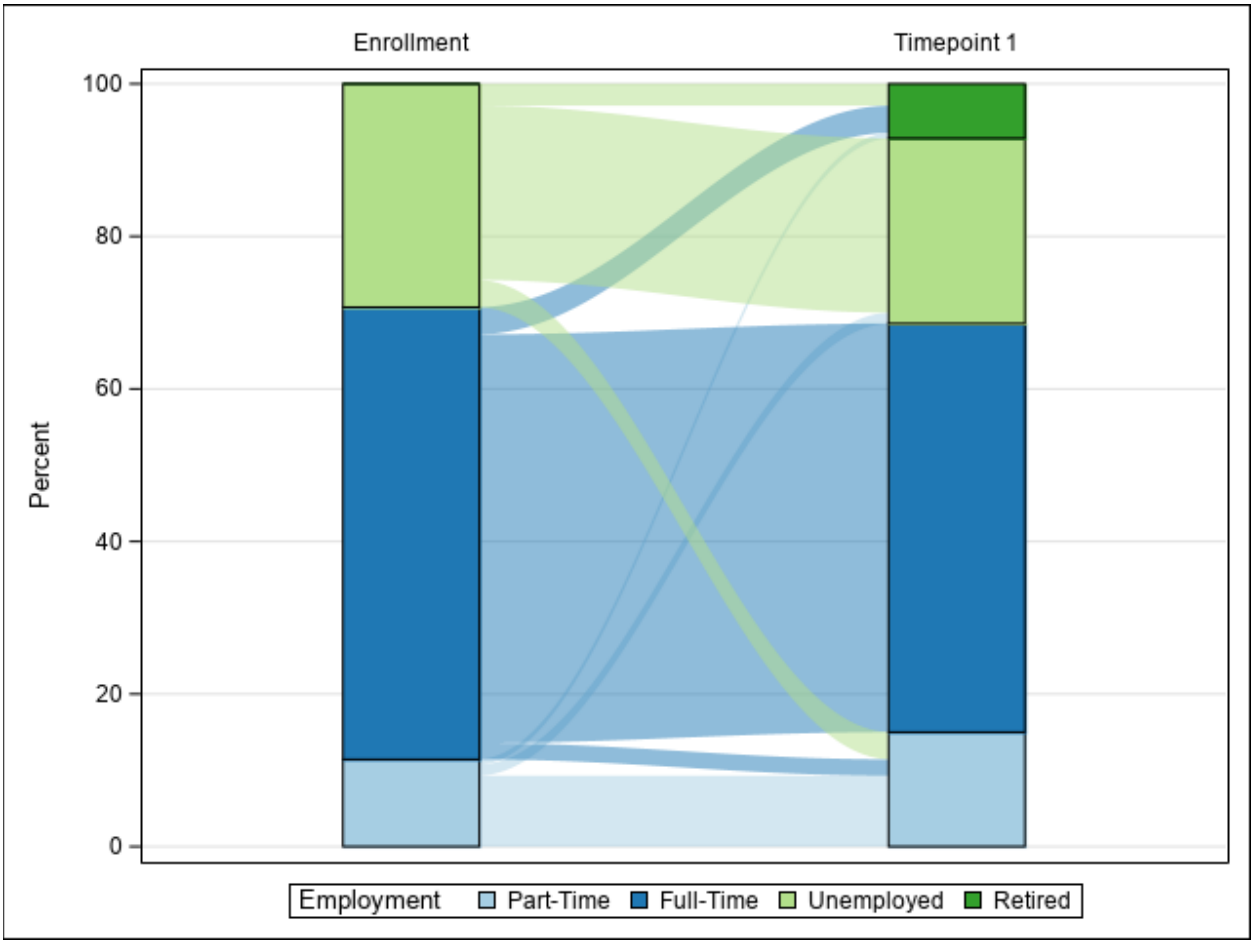
[e]A higher ECDSS score indicates worse symptom severity.

[f]A higher financial burden score indicates worse burden.

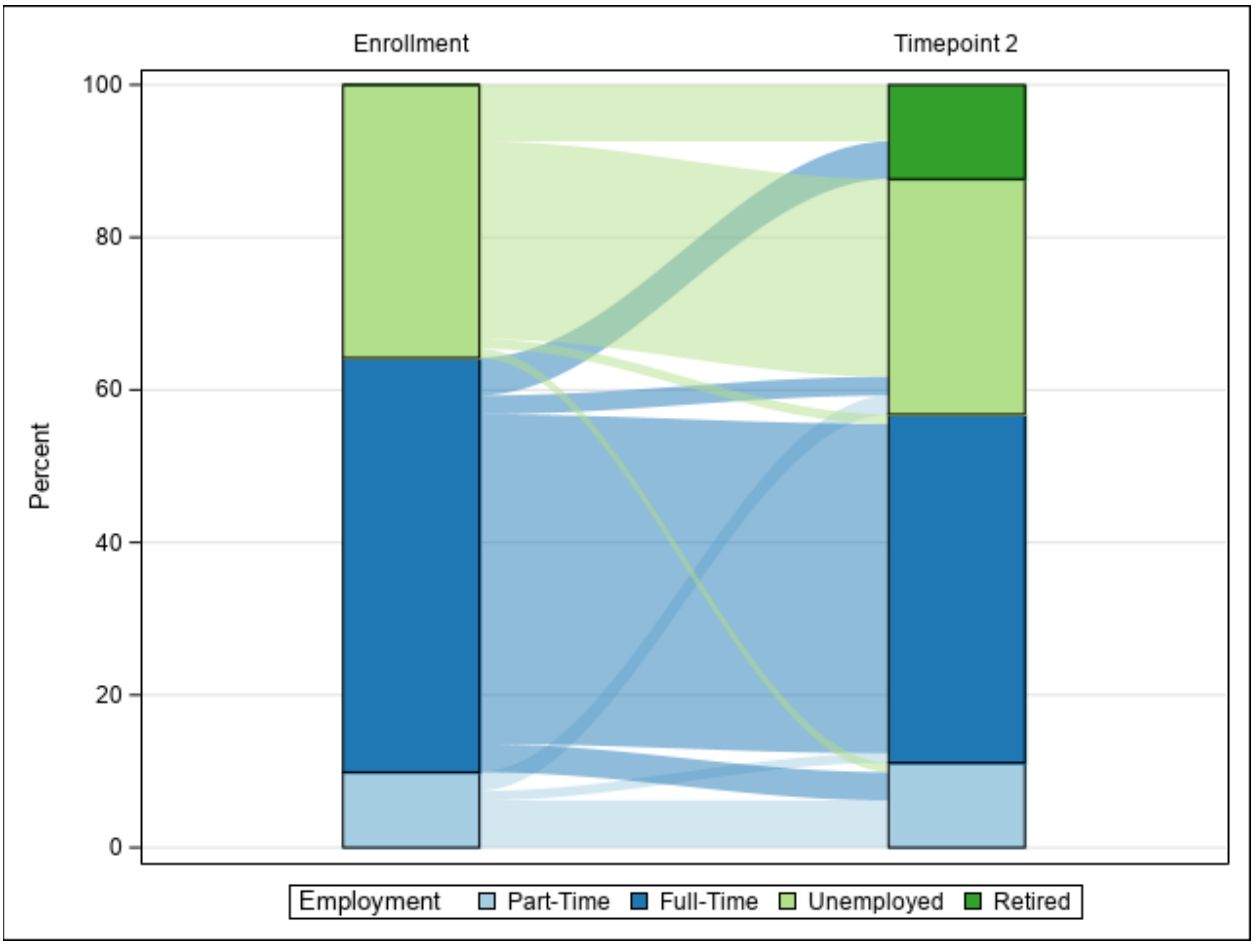
[g]A higher FACT-Cog subscale or total score indicates better cognitive functioning.

Supplemental Figure 1: Distribution of employment status changes over time.
A) from enrollment to Timepoint 1. B) from enrollment to Timepoint 2.

A



B


Enrollment
Timepoint 2
100
80
60
40
20
0
Percent
Employment
Part-Time
Full-Time
Unemployed
Retired