Patient-Reported Outcomes in Huntington Disease: Neuro-QOL and HDQLIFE Physical Function Measures

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Background: There is a need for patient reported outcome measures that capture the impact that motor impairments have on health-related quality of life in individuals with Huntington disease.

Objectives: Establish the reliability and validity of new physical functioning patient reported outcome measures in Huntington disease.

Methods: 510 individuals with Huntington disease completed two Quality of Life in Neurological Disorders ("Neuro-QoL" Lower Extremity Function and Upper Extremity Function) and three Huntington Disease Health-Related Quality of Life ("HDQLIFE" Chorea, Speech Difficulties, and Swallowing Difficulties) measures. Clinician-rated and generic self-report measures were also administered.

Results: Reliabilities for the new patient reported physical functioning measures were excellent (all Cronbach's $\alpha > .92$). Convergent, discriminant validity and known groups validity was supported.

Conclusions: Results provide psychometric support for the new patient reported physical functioning measures and that these measures can be used as clinically meaningful endpoints in Huntington disease research and clinical practice.

Huntington disease (HD) is a progressive neurodegenerative disorder that causes profound cognitive, behavioral, and motor decline. The motor phenomenology in HD is multifaceted and affects all body segments and limbs, with profound impacts on daily living and social participation. The most characteristic and best studied motor symptom in HD is chorea.[1-4] Chorea is associated with falls, gait disturbance and balance difficulties.[5-10] By mid- to late-stage HD, even if chorea is controlled, a host of less treatable motor problems steadily worsen (dystonia, bradykinesia, rigidity, and ataxia). Motor symptoms also affect oropharyngeal function resulting in worsening dysarthria[11-13] and dysphagia.[14]

Patient-reported outcome (PRO) measures about motor symptoms and associated activity limitations are rarely used in HD trials, even though such outcomes are increasingly recognized as important measures of efficacy for new treatments.[15] In a devastating disease like HD, where intensive treatment efforts are directed at the development of treatments designed to improve physical activity engagement,[16-21] there is a particular need for meaningful and sensitive PRO measures that capture these aspects of health-related quality of life (HRQOL).

The HDQLIFE measurement system[22-25] was designed to provide reliable and valid assessments of HRQOL among individuals with HD. This system includes several HD-specific measures of HRQOL, as well as generic HRQOL measures from the Quality of Life in Neurological Disorders [Neuro-QoL] system.[26, 27] The goal of this paper is to provide reliability and validity data for the HDQLIFE PROs that evaluate physical function.

Methods

Participants

Individuals with either prodromal (gene-positive status for the HD CAG expansion and no clinical diagnosis) or manifest HD were invited to participate in this study. Participants were ≥18 years of age, able to read and understand English, and had the ability to provide informed

consent. Participants were recruited through specialized HD treatment centers, the HD Roster, existing data capture systems,[28] and the Predict-HD research study.[29]

Measures.

We examined Neuro-QoL Lower Extremity Function and Neuro-QoL Upper Extremity Function[19,29] computer adaptive tests (CATs) and fixed 8-item short-forms (SFs). We also examined simulated CAT and 6-item SF scores for HDQLIFE Chorea,[30] HDQLIFE Speech Difficulties,[31] and HDQLIFE Swallowing Difficulties.[31] Resulting scores are on a *t*-metric (*M*=50, *SD*=10).

Composite Scores. Upper and lower extremity composite scores were created by the a *priori* selection of self-rated and clinician-rated items. The *upper extremity self-rated composite* was comprised of the EuroQoL 5 Dimensions Questionnaire (EQ5D)[32] self-care item, one Veterans Rand 12-item Health Status Inventory[33] item ("Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?"), two World Health Organization Disability Assessment Schedule 2.0 (WHODAS)[34] items ("In the last 30 days, how much difficulty did you have in: Washing your whole body?" and "In the last 30 days, how much difficulty did you have in: Getting dressed?"), and items from a self-report version of the UHDRS[35] Total Functional Capacity (TFC; "Are you able to work;" Are you able to manage your own finances;" "Are you able to complete household chores without help;" "Are you able to accomplish daily living tasks, such as bathing, dressing, and meal preparation without help;" "What type of care do you receive?"). Self-reported TFC internal consistency (Cronbach's α=0.86) and convergent validity with the clinician-rated version (ICC=0.89; 95% CI:.87,.91) were supported. The *lower extremity self-rated composite* was comprised of the EQ5D[32] mobility item, one Rand[33] item ("Does your health now limit you in climbing several flights of stairs? If so, how much?"), two WHODAS[34] items ("In the last 30 days, how much difficulty did you have in: standing for long periods such as 30 minutes;" and "In the last 30 days, how much difficulty did you have in: walking a long distance, such as a kilometer

(or equivalent)?"), and the self-reported TFC items. The *upper extremity clinician-rated composite* was comprised of the UHDRS[35] Independence Scale, TFC score, and Motor Assessment upper extremity items (finger tapping, pronation and hand supination, Luria, arm rigidity, upper extremity dystonia, upper extremity chorea). The *lower extremity clinician-rated composite* was comprised of the Independence Scale, TFC score, and Motor Assessment lower extremity items (gait, tandem walking, retropulsion, lower extremity dystonia, lower extremity chorea). All composite scores were coded so that higher scores indicated worse function; scores were transformed to z scores, averaged, and transformed to *t*-scores (*M*=50, *SD*=10).

Clinician-rated TFC was used to classify manifest HD participants as either early-stage (sum scores of 7-13) or late-stage (sum scores of 0-6).[36]

Analyses.

Internal Consistency Reliability, Convergent and Discriminant Validity. A multi-trait multi-method correlation matrix where Pearson correlation coefficients are organized such that each method (PRO and Composite Measures) is arranged corresponding to different concepts (clinician-ratings or self-reported), was used to examine internal consistency reliability (Cronbach's alphas) and determine associations among PROs, self-rated, and clinician-rated composites. Coefficients on the diagonal provide estimated reliabilities. Coefficients between similar methods and concepts (e.g., PRO vs. PRO composite) should yield the strongest relationships (correlations ≥0.6 support convergent validity), and coefficients between different methods and concepts (e.g., PRO vs. Clinician Composite) should yield the weakest relationships (03 to 0.6 correlations support discriminant validity).[37]

Known-Groups Analyses. Multivariate analyses were conducted to identify group differences (prodromal, early-, late-HD). Prodromal participants should report better functioning than both manifest HD groups; early-HD participants should report better functioning than late-HD participants.

Effect sizes. Cohen's d were calculated to evaluate the relative influence that symptom severity (determined by a median split using the corresponding clinician-rated scores/item[s] from the UHDRS Motor Assessment) had on self-reported physical functioning. Neuro-QOL scores were compared to the UHDRS Total Motor score, HDQLIFE Chorea was compared to the clinician-rated UHDRS Motor Assessment chorea items, HDQLIFE Speech Difficulties was compared to the clinician-rated UHDRS Motor Assessment speech item, and HDQLIFE Swallowing Difficulties was compared to the clinician-rated UHDRS Motor Assessment swallowing item. Effect sizes for the Neuro-QoL PROs were examined relative to the Neuro-QoL normative sample (N=1046 for Lower Extremity; N=1095 for Upper Extremity; *M*=50, *SD*=10); effect sizes for each HDQLIFE PRO was examined relative to this sample. The largest effect sizes should be seen among those with greater clinician-rated severity.

Classification Accuracy (Sensitivity/Specificity). Logistic regression models were conducted to determine the accuracy with which the PROs could discriminate between different HD groups. Likelihood ratios for clinical decision making should be ≥2.[38] Receiver Operating Characteristic analysis was used to compare diagnostic performance of the PROs (minimal acceptable area under the curve specified as ≥.70.[39]

Results

Five-hundred-ten individuals with prodromal (*n*=198), early- (*n*=195) or late-stage HD (n=117) participated in this study. Participants ranged from 18-81 years of age (*M*=49.10, *SD*=13.23), 59.2% of participants were female, and the majority of participants were Caucasian (96.1%). Education ranged from 4-26 years (*M*=15.06, *SD*=2.89). Descriptive data for the PROs is provided in Table 1. An examination of floor effects by group (prodromal, early-, and late-stage HD) confirmed that floor effects were most prevalent in the prodromal group (of those with floor effects ≥65% were prodromal participants).

Internal Consistency Reliability, Convergent and Discriminant Validity. Reliability coefficients (in italics) for the Neuro-QoL (both=0.97) and HDQLIFE measures were excellent

(.98 for Chorea and Speech, .97 for Swallowing; Table 1). Validity coefficients (in bold) were higher between the Neuro-QoL/HDQLIFE measures and the composite self-report measures than they were with the clinician-rated composites supporting convergent and discriminant validity, respectively.

Known-Groups Analyses. Analyses indicated significant group differences among all three groups; findings were in the predicted direction (Table 2).

Effect sizes. As expected, effect sizes were larger for the groups with more clinician-rated severity (Table 2).

Classification Accuracy (Sensitivity/Specificity). Classification accuracy was generally moderate to high for all PROs when differentiating between prodromal-HD and either manifest HD group (Table 2).

Discussion

Results support the reliability and validity of the Neuro-QoL and HDQLIFE physical functioning PROs in individuals with prodromal and manifest HD. Specifically, results provided strong support for the internal consistency reliability of the PROs, and while there was some evidence of floor effects (which reflected the fact that the majority of the prodromal group was not exhibiting motor problems) these PROs were free of ceiling effects. Convergent and discriminant validity of the PROs were also supported. Specifically, convergent validity was supported by strong associations between the physical functioning PROs and other measures of self-reported physical functioning, and discriminant validity was supported by slightly smaller associations between the PROs and the clinician-rated composites.

As expected, we also found that individuals with prodromal HD had less physical dysfunction than either manifest HD group and that individuals with late-HD had more severe motor functional impairments than early-HD. Furthermore, effect sizes for the PROs were higher for participants with lower clinician-rated functioning than those with better functioning. Together, these findings support the construct validity of these new measures in HD.

Finally, moderate to high sensitivity and specificity were found for almost all the new PROs. In particular, scores on all PROs suggested that they could be used to discriminate between individuals with prodromal and early-HD, and between prodromal and late-HD (except HDQLIFE Swallowing Difficulties), suggesting that these measures may be especially sensitive to tracking disease progression over time.

While this study provides important psychometric support for these new PROs, there are limitations to this study. First, participants were recruited through other research studies and through established HD clinics; this convenience sample may not represent the HD population at large. Further, multi-trait, multi-method analyses relied on composite scores that were generated using individual items from existing scales and self-report versions of clinician-administered measures. This departure from their intended use and/or standardized administration may either over- or underestimate the participants' "true" abilities, which could potentially weaken the interpretation of this validity data. Finally, symptom progression in HD includes cognitive impairments[40-45] and anosognosia (lack of self-awareness)[46] that may preclude the ability to examine HRQOL using PROs. Regardless, such self-report measures should be used in conjunction with other information (e.g., performance-based and clinician-rated assessments) when making clinical decisions, especially among individuals that are later in the disease process.

The Neuro-QoL and HDQLIFE PROs provide brief, reliable, and valid assessments of physical functioning. Furthermore, these PROs are able to differentiate between individuals with prodromal versus early- or late-stage HD. As such, these measures fill a significant gap in HD clinical interventions where sensitive PROs are needed to detect improvements in motor impairment and physical activity engagement.

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CONFLICTS OF INTEREST:

Carlozzi, N.E. currently has research grants from the NIH; she is also supported by grant funding from the NIH and CHDI. She provides patient reported outcome measurement selection and application consultation for Teva Pharmaceuticals.

Ready, R.E. declares that she has no conflicts of interest.

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Table 1

Multi-trait multi-method correlation matrix and descriptive data for Neuro-QoL and HDQLIFE physical function measures

	NQ Lower Extremity Function	NQ Upper Extremity Function	HDQLIFE Chorea	HDQLIFE Speech Difficulties	HDQLIFE Swallowing Difficulties	Lower Extremity Composite - Clinician	Upper Extremity Composite- Clinician	Chorea Composite - Clinician	Speech/ Swallowing Composite - Clinician	Lower Extremity Composite - Self	Upper Extremity Composite - Self
PRO Measure											
NQ Lower Extremity Function	*0.97*										
NQ Upper Extremity Function	0.79	*0.97*									
HDQLIFE Chorea	-0.78	-0.77	*0.98*								
HDQLIFE Speech Difficulties	-0.70	-0.68	0.77	*0.98*							
HDQLIFE Swallowing Difficulties	-0.66	-0.66	0.70	0.69	*0.97*						
Composite Measure											
Lower Extremity Composite - Clinician	**0.68**	0.72	**-0.66**	-0.55	-0.51	*0.92*					
Upper Extremity Composite- Clinician	0.63	**0.71**	**-0.65**	-0.54	-0.50	0.92	*0.94*				
Chorea Composite - Clinician	0.50	0.53	**-0.60**	-0.47	-0.44	0.73	0.73	*0.95*			
Speech/Swallowing Composite - Clinician	0.53	0.63	-0.54	**-0.47**	**-0.40**	0.79	0.83	0.57	*0.76*		
Lower Extremity Composite - Self	**0.83**	0.77	**-0.77**	-0.65	-0.62	**0.76**	0.73	**0.48**	0.64	*0.91*	
Upper Extremity Composite - Self	0.73	**0.77**	**-0.72**	-0.65	-0.61	0.72	**0.70**	**0.40**	0.64	0.85	*0.84*
Descriptive Data											
CAT *M*	48.78	44.79	49.12	48.27	49.50	--	--	--	--	--	--
CAT (*SD*)	(10.61)	(10.70)	(9.30)	(8.89)	(8.73)	--	--	--	--	--	--
SF *M*	49.25	44.71	49.62	48.52	49.43	50.06	50.05	50.00	50.03	50.12	50.20
SF (*SD*)	(9.66)	(10.63)	(8.52)	(8.58)	(8.61)	(7.74)	(7.62)	(8.81)	(8.95)	(8.43)	(7.55)
Cronbach's α (SF only)	0.93	0.94	0.93	0.93	0.92	0.92	0.94	0.95	0.76	0.91	0.84
CAT % with floor effects (high function)	27.2	35.2	27.4	22.4	35.1	--	--	--	--	--	--
CAT % with ceiling effects (low function)	0.2	0.6	0.2	0.6	0.6	--	--	--	--	--	--
SF % with floor effects (high function)	41.5	51.8	50.4	30.1	44.6	5.4	2.6	26.9	52.3	26.6	30.3
SF % with ceiling effects (low function)	0.2	0.2	0.0	0.0	0.0	0.2	0.2	0.4	0.2	0.2	0.6
Administration Time (sec) Median (SD)	66 (65)	69 (79)	48 (40)	34 (40)	59 (84)	--	--	--	--	--	--

Note. Correlations are reported for computer adaptive test administrations; Reliability coefficients are provided in italics and validity coefficients are provided in bold; all $p < 0.01$ level (2-tailed); NQ = Neuro-QoL; PRO = patient reported outcome; CAT = computer adaptive test; SF = Short Form; sec = seconds

Table 2

Known-groups validity, effect sizes, and classification accuracy of the new patient reported outcome computer adaptive tests

Known Groups Validity	Prodromal HD (N=197)		Early-HD (N=188)		Late-HD (N=106)		*F*	*Partial eta2*	Clinician Rated Severity on UHDRS Motor Exam item(s)	
	Mean	SD	Mean	SD	Mean	SD			*Low*	*High*
Lower Extremity Function/Mobility[a,b,c]	56.07	7.33	46.92	8.91	0.401	8.59	163.021	0.401	-0.71	0.52
Upper Extremity Function - Fine Motor ADL[a,b,c]	52.49	6.60	43.24	8.85	0.467	7.98	214.214	0.467	-1.15	0.12

Known Group Validity	Prodromal HD (N=194)		Early-HD (N=191)		Late-HD (N=106)		*F*	*Partial eta2*	Clinician Rated Severity on UHDRS Motor Exam item(s)	
	Mean	SD	Mean	SD	Mean	*Low*			*Low*	*High*
HDQLIFE Chorea[a,b,c]	43.43	3.80	51.64	7.83	0.391	8.27	156.978	0.391	1.40	-0.09
HDQLIFE Speech Difficulties[a,b,c]	42.87	6.16	50.29	7.56	0.309	7.62	109.143	0.309	2.20	-0.19
HDQLIFE Swallowing Difficulties[a,b,c]	44.17	5.70	51.03	8.19	0.296	7.97	102.354	0.296	0.44	-0.06

Classification Accuracy	Prodromal vs. Early			Prodromal vs. Late			Early vs. Late		
	Sensitivity, Specificity	Area Under the Curve	Likelihood Ratio	Sensitivity, Specificity	Area Under the Curve	Likelihood Ratio	Sensitivity, Specificity	Area Under the Curve	Likelihood Ratio

Lower Extremity Function/Mobility	70.2, 72.1	0.78	2.36	86.8, 92.9	0.95	6.58	55.7, 82.4	0.80	1.26
Upper Extremity Function - Fine Motor ADL	72.3, 70.6	0.78	2.61	77.6, 88.8	0.93	3.46	52.3, 85.1	0.75	1.10
HDQLIFE Chorea	82.2, 79.6	0.86	4.62	77.2, 91.6	0.92	3.39	22.8, 91.4	0.67	0.30
HDQLIFE Speech Difficulties	70.7, 69.9	0.78	2.41	70.0, 87.0	0.87	2.33	24.5, 92.7	0.66	0.32
HDQLIFE Swallowing Difficulties	68.1, 71.6	0.74	2.13	60.7, 84.5	0.84	1.54	17.9, 92.7	0.62	0.22

Note. All $p < .0001$; HD = Huntington disease; CAT = computer adaptive test; ADL = activities of daily living; there were significant differences among all three groups for all Neuro-QoL and HDQLIFE measures

[a] indicates significant differences between prodromal and early-HD
[b] indicates significant differences between prodromal and late-HD
[c] indicates significant differences between early-HD and late-HD

Patient-Reported Outcomes in Huntington Disease: Neuro-QOL and HDQLIFE Physical Function Measures

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Key Words: Neuro-QoL; HDQLIFE; Huntington disease; physical functioning; chorea; motor symptoms; health-related quality of life; patient reported outcome (PRO)

Background: There is a need for patient reported outcome measures that capture the impact that motor impairments have on health-related quality of life in individuals with Huntington disease.

Objectives: Establish the reliability and validity of new physical functioning patient reported outcome measures in Huntington disease.

Methods: 510 individuals with Huntington disease completed two Quality of Life in Neurological Disorders ("Neuro-QoL" Lower Extremity Function and Upper Extremity Function) and three Huntington Disease Health-Related Quality of Life ("HDQLIFE" Chorea, Speech Difficulties, and Swallowing Difficulties) measures. Clinician-rated and generic self-report measures were also administered.

Results: Reliabilities for the new patient reported physical functioning measures were excellent (all Cronbach's $\alpha > .92$). Convergent, discriminant validity and known groups validity was supported.

Conclusions: Results provide psychometric support for the new patient reported physical functioning measures and that these measures can be used as clinically meaningful endpoints in Huntington disease research and clinical practice.

Huntington disease (HD) is a progressive neurodegenerative disorder that causes profound cognitive, behavioral, and motor decline. The motor phenomenology in HD is multifaceted and affects all body segments and limbs, with profound impacts on daily living and social participation. The most characteristic and best studied motor symptom in HD is chorea.[1-4] Chorea is associated with falls, gait disturbance and balance difficulties.[5-10] By mid- to late-stage HD, even if chorea is controlled, a host of less treatable motor problems steadily worsen (dystonia, bradykinesia, rigidity, and ataxia). Motor symptoms also affect oropharyngeal function resulting in worsening dysarthria[11-13] and dysphagia.[14]

Patient-reported outcome (PRO) measures about motor symptoms and associated activity limitations are rarely used in HD trials, even though such outcomes are increasingly recognized as important measures of efficacy for new treatments.[15] In a devastating disease like HD, where intensive treatment efforts are directed at the development of treatments designed to improve physical activity engagement,[16-21] there is a particular need for meaningful and sensitive PRO measures that capture these aspects of health-related quality of life (HRQOL).

The HDQLIFE measurement system[22-25] was designed to provide reliable and valid assessments of HRQOL among individuals with HD. This system includes several HD-specific measures of HRQOL, as well as generic HRQOL measures from the Quality of Life in Neurological Disorders [Neuro-QoL] system.[26, 27] The goal of this paper is to provide reliability and validity data for the HDQLIFE PROs that evaluate physical function.

Methods

Participants

Individuals with either prodromal (gene-positive status for the HD CAG expansion and no clinical diagnosis) or manifest HD were invited to participate in this study. Participants were ≥18 years of age, able to read and understand English, and had the ability to provide informed

consent. Participants were recruited through specialized HD treatment centers, the HD Roster, existing data capture systems,[28] and the Predict-HD research study.[29]

Measures.

We examined Neuro-QoL Lower Extremity Function and Neuro-QoL Upper Extremity Function[19,29] computer adaptive tests (CATs) and fixed 8-item short-forms (SFs). We also examined simulated CAT and 6-item SF scores for HDQLIFE Chorea,[30] HDQLIFE Speech Difficulties,[31] and HDQLIFE Swallowing Difficulties.[31] Resulting scores are on a *t*-metric (*M*=50, *SD*=10).

Composite Scores. Upper and lower extremity composite scores were created by the a *priori* selection of self-rated and clinician-rated items. The *upper extremity self-rated composite* was comprised of the EuroQoL 5 Dimensions Questionnaire (EQ5D)[32] self-care item, one Veterans Rand 12-item Health Status Inventory[33] item ("Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?"), two World Health Organization Disability Assessment Schedule 2.0 (WHODAS)[34] items ("In the last 30 days, how much difficulty did you have in: Washing your whole body?" and "In the last 30 days, how much difficulty did you have in: Getting dressed?"), and items from a self-report version of the UHDRS[35] Total Functional Capacity (TFC; "Are you able to work;" Are you able to manage your own finances;" "Are you able to complete household chores without help;" "Are you able to accomplish daily living tasks, such as bathing, dressing, and meal preparation without help;" "What type of care do you receive?"). Self-reported TFC internal consistency (Cronbach's α=0.86) and convergent validity with the clinician-rated version (ICC=0.89; 95% CI:.87,.91) were supported. The *lower extremity self-rated composite* was comprised of the EQ5D[32] mobility item, one Rand[33] item ("Does your health now limit you in climbing several flights of stairs? If so, how much?"), two WHODAS[34] items ("In the last 30 days, how much difficulty did you have in: standing for long periods such as 30 minutes;" and "In the last 30 days, how much difficulty did you have in: walking a long distance, such as a kilometer

(or equivalent)?"), and the self-reported TFC items. The *upper extremity clinician-rated composite* was comprised of the UHDRS[35] Independence Scale, TFC score, and Motor Assessment upper extremity items (finger tapping, pronation and hand supination, Luria, arm rigidity, upper extremity dystonia, upper extremity chorea). The *lower extremity clinician-rated composite* was comprised of the Independence Scale, TFC score, and Motor Assessment lower extremity items (gait, tandem walking, retropulsion, lower extremity dystonia, lower extremity chorea). All composite scores were coded so that higher scores indicated worse function; scores were transformed to z scores, averaged, and transformed to *t*-scores (*M*=50, *SD*=10).

Clinician-rated TFC was used to classify manifest HD participants as either early-stage (sum scores of 7-13) or late-stage (sum scores of 0-6).[36]

Analyses.

Internal Consistency Reliability, Convergent and Discriminant Validity. A multi-trait multi-method correlation matrix where Pearson correlation coefficients are organized such that each method (PRO and Composite Measures) is arranged corresponding to different concepts (clinician-ratings or self-reported), was used to examine internal consistency reliability (Cronbach's alphas) and determine associations among PROs, self-rated, and clinician-rated composites. Coefficients on the diagonal provide estimated reliabilities. Coefficients between similar methods and concepts (e.g., PRO vs. PRO composite) should yield the strongest relationships (correlations ≥0.6 support convergent validity), and coefficients between different methods and concepts (e.g., PRO vs. Clinician Composite) should yield the weakest relationships (03 to 0.6 correlations support discriminant validity).[37]

Known-Groups Analyses. Multivariate analyses were conducted to identify group differences (prodromal, early-, late-HD). Prodromal participants should report better functioning than both manifest HD groups; early-HD participants should report better functioning than late-HD participants.

Effect sizes. Cohen's d were calculated to evaluate the relative influence that symptom severity (determined by a median split using the corresponding clinician-rated scores/item[s] from the UHDRS Motor Assessment) had on self-reported physical functioning. Neuro-QOL scores were compared to the UHDRS Total Motor score, HDQLIFE Chorea was compared to the clinician-rated UHDRS Motor Assessment chorea items, HDQLIFE Speech Difficulties was compared to the clinician-rated UHDRS Motor Assessment speech item, and HDQLIFE Swallowing Difficulties was compared to the clinician-rated UHDRS Motor Assessment swallowing item. Effect sizes for the Neuro-QoL PROs were examined relative to the Neuro-QoL normative sample (N=1046 for Lower Extremity; N=1095 for Upper Extremity; *M*=50, *SD*=10); effect sizes for each HDQLIFE PRO was examined relative to this sample. The largest effect sizes should be seen among those with greater clinician-rated severity.

Classification Accuracy (Sensitivity/Specificity). Logistic regression models were conducted to determine the accuracy with which the PROs could discriminate between different HD groups. Likelihood ratios for clinical decision making should be ≥2.[38] Receiver Operating Characteristic analysis was used to compare diagnostic performance of the PROs (minimal acceptable area under the curve specified as ≥.70.[39]

Results

Five-hundred-ten individuals with prodromal (*n*=198), early- (*n*=195) or late-stage HD (n=117) participated in this study. Participants ranged from 18-81 years of age (*M*=49.10, *SD*=13.23), 59.2% of participants were female, and the majority of participants were Caucasian (96.1%). Education ranged from 4-26 years (*M*=15.06, *SD*=2.89). Descriptive data for the PROs is provided in Table 1. An examination of floor effects by group (prodromal, early-, and late-stage HD) confirmed that floor effects were most prevalent in the prodromal group (of those with floor effects ≥65% were prodromal participants).

Internal Consistency Reliability, Convergent and Discriminant Validity. Reliability coefficients (in italics) for the Neuro-QoL (both=0.97) and HDQLIFE measures were excellent

(.98 for Chorea and Speech, .97 for Swallowing; Table 1). Validity coefficients (in bold) were higher between the Neuro-QoL/HDQLIFE measures and the composite self-report measures than they were with the clinician-rated composites supporting convergent and discriminant validity, respectively.

Known-Groups Analyses. Analyses indicated significant group differences among all three groups; findings were in the predicted direction (Table 2).

Effect sizes. As expected, effect sizes were larger for the groups with more clinician-rated severity (Table 2).

Classification Accuracy (Sensitivity/Specificity). Classification accuracy was generally moderate to high for all PROs when differentiating between prodromal-HD and either manifest HD group (Table 2).

Discussion

Results support the reliability and validity of the Neuro-QoL and HDQLIFE physical functioning PROs in individuals with prodromal and manifest HD. Specifically, results provided strong support for the internal consistency reliability of the PROs, and while there was some evidence of floor effects (which reflected the fact that the majority of the prodromal group was not exhibiting motor problems) these PROs were free of ceiling effects. Convergent and discriminant validity of the PROs were also supported. Specifically, convergent validity was supported by strong associations between the physical functioning PROs and other measures of self-reported physical functioning, and discriminant validity was supported by slightly smaller associations between the PROs and the clinician-rated composites.

As expected, we also found that individuals with prodromal HD had less physical dysfunction than either manifest HD group and that individuals with late-HD had more severe motor functional impairments than early-HD. Furthermore, effect sizes for the PROs were higher for participants with lower clinician-rated functioning than those with better functioning. Together, these findings support the construct validity of these new measures in HD.

Finally, moderate to high sensitivity and specificity were found for almost all the new PROs. In particular, scores on all PROs suggested that they could be used to discriminate between individuals with prodromal and early-HD, and between prodromal and late-HD (except HDQLIFE Swallowing Difficulties), suggesting that these measures may be especially sensitive to tracking disease progression over time.

While this study provides important psychometric support for these new PROs, there are limitations to this study. First, participants were recruited through other research studies and through established HD clinics; this convenience sample may not represent the HD population at large. Further, multi-trait, multi-method analyses relied on composite scores that were generated using individual items from existing scales and self-report versions of clinician-administered measures. This departure from their intended use and/or standardized administration may either over- or underestimate the participants' "true" abilities, which could potentially weaken the interpretation of this validity data. Finally, symptom progression in HD includes cognitive impairments[40-45] and anosognosia (lack of self-awareness)[46] that may preclude the ability to examine HRQOL using PROs. Regardless, such self-report measures should be used in conjunction with other information (e.g., performance-based and clinician-rated assessments) when making clinical decisions, especially among individuals that are later in the disease process.

The Neuro-QoL and HDQLIFE PROs provide brief, reliable, and valid assessments of physical functioning. Furthermore, these PROs are able to differentiate between individuals with prodromal versus early- or late-stage HD. As such, these measures fill a significant gap in HD clinical interventions where sensitive PROs are needed to detect improvements in motor impairment and physical activity engagement.

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CONFLICTS OF INTEREST:

Carlozzi, N.E. currently has research grants from the NIH; she is also supported by grant funding from the NIH and CHDI. She provides patient reported outcome measurement selection and application consultation for Teva Pharmaceuticals.

Ready, R.E. declares that she has no conflicts of interest.

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