

# Challenges Assessing Functional Outcomes in Early Huntington Disease



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## BACKGROUND:

A major challenge for the neurodegenerative disorders has been the identification of clinical outcome measures that accurately track disease. Primary outcome measures used in Huntington disease (HD) clinical trials typically involve a clinical symptom or sign (usually chorea) and a measure of everyday function. Since the advent of genetic testing for HD, it is possible to identify gene carriers prior to the onset of clinical symptoms, which opens up the possibility of clinical trials of disease-modifying treatments in clinically asymptomatic or minimally-symptomatic persons.

It is unknown whether typical clinical endpoints designed for manifest motor disease are sensitive in earlier stages of disease. The primary aim of this study was to evaluate traditional patient-reported outcomes in the earliest-studied HD participants likely to be recruited into clinical trials.

## METHODS/TECHNIQUES:

Traditional functional capacity measures were examined in 786 “pre-HD” (gene-positive but not clinically diagnosed) participants recruited for the PREDICT-HD study.

## RESULTS/OUTCOMES:

Functional capacity measures were not sensitive for HD in very early stages; over 88% scored at ceiling. Prospective evaluation revealed that the first functional loss in this population was in the area of performance in their accustomed work. In a survival analysis, motor, cognitive and psychiatric measures were all predictors of job change in pre-HD.

## CONCLUSIONS:

To our knowledge, this is the first prospective study ever conducted on the emergence of functional loss secondary to brain disease. We conclude that future clinical trials designed for very early disease will require the development of new and more sensitive measures of real-life function.

**Table 1: Logistic regression for engagement in accustomed work**

	Point Estimate	Estimate	S.E.	Chi-Square	p-value
SDMT	1.057	0.0555	0.0156	12.6604	0.0004
BDI Energy	0.707	-0.3468	0.0700	24.5752	<.0001
BDI Mood	0.954	-0.0472	0.0321	2.1590	0.1417
Motor Total	0.914	-0.0896	0.0242	13.7366	0.0002

n=775; BDI=Beck Depression Inventory; SDMT=Symbol Digit Modality Test

**Table 2: Rates of change on clinical outcome measures in pre-HD**

	Near Diagnosis		Mid Diagnosis		Far Diagnosis	
	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value
FAS	-0.143 (.02)	<.0001	-0.06 (.02)	.004	-0.02 (.018)	.26
TFC	-0.142 (.02)	<.0001	-0.046 (.02)	.02	-0.017 (.02)	.37
BDI	.014 (.17)	.93	-0.67 (.15)	<.0001	-0.27 (.15)	.07
BDI Mood	-0.019 (.09)	.83	-0.19 (.08)	.02	-0.09 (.08)	.26
BDI Energy	-0.07 (.04)	.11	-0.24 (.04)	<.0001	-0.12 (.04)	.003
SDMT	-0.77 (.18)	<.0001	.15 (.16)	.35	.75 (.16)	<.0001
Motor Total	1.69 (.14)	<.0001	.64 (.13)	<.0001	.27 (.12)	.03

FAS=Functional Assessment Scale; TFC=Total Functional Capacity; BDI=Beck Depression Inventory; SDMT=Symbol Digit Modality Test

**Table 3: Survival analysis for loss of accustomed work with baseline predictors**

	Estimate	S.E.	Chi Square	p-value	Hazard Ratio
BDI mood	-0.028	0.03	0.86	.3525	0.972
BDI energy	0.234	0.057	17.08	<.0001	1.264
SDMT	-0.046	0.011	16.57	<.0001	0.955
Motor Total	0.062	0.016	15.56	.0001	1.065

N=643 with all data; BDI=Beck Depression Inventory; SDMT=Symbol Digit Modality Test

**Table 4: Percent and number of pre-HD participants not endorsing maximum scores on items from the FAS and TFC.**

FAS Item	Percent	N
Could participant engage in gainful employment in his/her accustomed work?	7.7	60 <sup>a</sup>
Could participant engage in any kind of gainful employment?	2.8	22 <sup>a</sup>
Could participant manage his/her finances (monthly) without any help?	2.2	17 <sup>a</sup>
Could participant operate an automobile safely and independently?	1.3	10 <sup>a</sup>
Could participant engage in any kind of volunteer or non-gainful work?	1.0	8 <sup>a</sup>
Could participant shop for groceries without help?	.5	4 <sup>a</sup>
Could participant use public transportation to get places without help?	.5	4 <sup>a</sup>
TFC Item		
OCCUPATION: 3=normal		
2=reduced capacity for usual job	5.5	43 <sup>b</sup>
1,0=marginal work and unable	2.8	23 <sup>b</sup>
FINANCES: 3=normal		
2=slight assistance	2.8	22 <sup>b</sup>
1, 0 =major assistance and unable	0.8	6 <sup>b</sup>
ADL: 3=normal		
2,1,0=minimal impairment and total care	2.3	18 <sup>b</sup>
DOMESTIC CHORES: 2=normal		
1,0=impaired and unable	1.0	8 <sup>b</sup>

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