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Prediction of manifest Huntington's disease with clinical and imaging measures: a prospective observational study

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Summary

Background **Although the association between cytosine-adenine-guanine (CAG) repeat length and age at onset of Huntington's disease is well known, improved prediction of onset would be advantageous for clinical trial design and prognostic counselling. We compared various measures for tracking progression and predicting conversion to manifest Huntington's disease.**

Methods **In this prospective observational study, we assessed the ability of 40 measures in five domains (motor, cognitive, psychiatric, functional, and imaging) to predict time to motor diagnosis of Huntington's disease, accounting for CAG repeat length, age, and the interaction of CAG repeat length and age. Eligible participants were individuals from the PREDICT-HD study (from 33 centres in six countries [USA, Canada, Germany, Australia, Spain, UK]) with the gene mutation for Huntington's disease but without a motor diagnosis (a rating below 4 on the diagnostic confidence level from the 15-item motor assessment of the Unified Huntington's Disease Rating Scale). Participants were followed up between September, 2002, and July, 2014. We used joint modelling of longitudinal and survival data to examine the extent to which baseline and change of measures analysed separately was predictive of CAG-adjusted age at motor diagnosis.**

Findings **1078 individuals with a CAG expansion were included in this analysis. Participants were followed up for a mean of 5·1 years (SD 3·3, range 0·0–12·0). 225 (21%) of these participants received a motor diagnosis of Huntington's disease during the study. 37 of 40 cross-sectional and longitudinal clinical and imaging measures were significant predictors of motor diagnosis beyond CAG repeat length and age. The strongest predictors were in the motor, imaging, and cognitive domains: an increase of one SD in total motor score (motor domain) increased the risk of a motor diagnosis by 3·07 times (95% CI 2·26–4·16), a reduction of one SD in putamen volume (imaging domain) increased risk by 3·32 times (2·37–4·65), and a reduction of one SD in Stroop word score (cognitive domain) increased risk by 2·32 times (1·88–2·87).**

Interpretation **Prediction of diagnosis of Huntington's disease can be improved beyond that obtained by CAG repeat length and age alone. Such knowledge about potential predictors of manifest Huntington's disease should inform discussions about guidelines for diagnosis, prognosis, and counselling, and might be useful in guiding the selection of participants and outcome measures for clinical trials.**

Funding **US National Institutes of Health, US National Institute of Neurological Disorders and Stroke, and CHDI Foundation.**

Introduction

Huntington's disease is an autosomal dominant neurodegenerative disease caused by expansion of the trinucleotide cytosine-adenine-guanine (CAG) in the first exon of the *Huntingtin* (*HTT*) gene. There is a well known association between the length of the CAG mutation and age at disease onset,[1] although substantial individual variation is evident. Over the past decade, results from the Neurobiological Predictors of Huntington's Disease study (PREDICT-HD; ClinicalTrials.gov number NCT00051324) and others[2–11] have documented disease-related changes of clinical features and biomarkers in people with the CAG expansion but not yet diagnosed with Huntington's disease.[12,13] If they are to be useful, clinical and biological markers should be predictive of landmark events, such as clinical motor diagnosis.

Improved predictability of Huntington's disease diagnosis could advance design of future studies, experimental trials, and clinical care through improved prognosis and earlier intervention. In this study, we compared genetic, demographic, motor, cognitive, psychiatric, functional, and imaging measures for the prediction of conversion to manifest Huntington's disease in people with CAG expansion.

Methods

Study design and participants

In this prospective observational study, we assessed the ability of various measures to predict time to motor diagnosis (first occurrence) in additon to CAG repeat length, age, and the interaction of CAG repeat length and age. Eligible participants were from 33 centres (in

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See Online for appendix

six countries [USA, Canada, Germany, Australia, Spain, and UK]) recruited to the PREDICT-HD study, had more than 35 *HTT* CAG repeats, had previous and independent genetic testing for Huntington's disease, and had less than the highest rating (ie, <4) on the diagnostic confidence level (DCL) of the Unified Huntington's Disease Rating Scale (UHDRS) at the beginning of the study. Exclusion criteria included presence of other CNS disease, injury, or developmental disorder, or evidence of an unstable medical or psychiatric illness. Full details of the exclusion criteria have been published previously.[14]

Control participants without a CAG expansion were included in an ancillary analysis to establish the variability and range of total motor score in participants without the gene mutation for Huntington's disease. All participants had to have independently undergone predictive testing for the Huntington's disease gene mutation, and those who had fewer than 36 repeats were classified as controls.

All participants provided written informed consent and were treated in accordance with the Declaration of Helsinki. The study was approved by institutional review boards at all participating institutions.

Procedures

Data for the longitudinal measures of interest were collected between September, 2002, and July, 2014. Findings were reviewed by the study executive committee (members listed in the appendix), who made decisions about use of the data in the study; if a control participant was seen to have a previously undetected neurological diagnosis, the participant and all of his or her data were excluded. All abnormalities in clinical and imaging data were forwarded to clinical investigators at the relevant study site for additional review and discussion. When the data were suggestive of abnormalities in function or brain imaging outside of the ranges reported in Huntington's disease, follow-up clinical investigations were encouraged.

We selected 40 longitudinal measures on the basis of their sensitivity to the detection and progression of Huntington's disease (appendix).[12] Motor measures were total motor score from the UHDRS and the chorea, bradykinesia, oculomotor, dystonia, and rigidity subdomains from the 15-item standardised UHDRS motor assessment. Cognitive measures were the Stroop colour and word test (three measures: word, colour, and interference), the Symbol Digit Modalities Test, the University of Pennsylvania Smell Identification Test, emotion recognition, speeded tapping, time production (also known as paced tapping), and the Trail Making Test (parts A and B). Psychiatric measures were the Global Distress Index and four subscales of the Symptom Checklist 90, the Beck Depression Inventory, and three subscales of the Frontal Systems Behavioral Scale. Imaging measures were intracranial-corrected volumes for putamen, accumbens, caudate, hippocampus, thalamus, globus pallidus, CSF, and lobar white and grey matter. Functional outcome measures were the total functional capacity and functional activity scale from the UHDRS, participant and companion ratings from the WHO Disability Assessment Schedule (version 2.0), and the Everyday Cognition rating scale (participant and companion ratings). Motor diagnosis of Huntington's disease was defined as a rating of 4 on the DCL of the UHDRS (ie, meets the operational definition of the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder in a person at risk for Huntington's disease, with ≥99% confidence). The DCL was administered by a movement disorder specialist after the 15-item standardised motor assessment.

Statistical analysis

We simultaneously modelled time to motor diagnosis and longitudinal change in the aforementioned variables using joint modelling for survival and longitudinal data (appendix).[15,16] The intention was to model progression to Huntington's disease diagnosis over the entire lifespan by use of the time metric of age adjusted for CAG expansion.

The survival model was a Cox regression model and the longitudinal model was a linear mixed-effects regression model. The time metric for both was age adjusted for genetic burden (CAG expansion), known as the CAG-Age Product (CAP; [age in years at baseline]×[CAG–33·66]).[17] CAP reflects the cumulative exposure to the effects of mutant huntingtin and is similar to other CAG-based and age-based measures.[18–20] We used CAP at motor diagnosis or censoring for the observation time in the Cox model, and CAP was the longitudinal time metric for the linear mixed-effects regression model. CAP as specified in this analysis is time-varying and represents age adjusted for CAG expansion. Because of the variability in age at study entry, the annual measurements span almost the entire adult age range, which allows inferences about motor diagnosis risk through life. The natural CAP intercept (baseline) is 0, denoting birth. Predictive power is meaningless at birth because the clinical measures have not been assessed. We chose the baseline CAP cross-section of 290 as the intercept because this is the value at which motor signs begin to appear in the PREDICT-HD cohort.[6] At this baseline, the putative predictive measures might have sufficient variability for an association with later motor diagnosis to be identified. A CAP value of 290 corresponds to the rounded ages of 40, 35, and 28 years for individuals with 41 CAG repeats (25th percentile), 42 repeats (median), and 44 repeats (75th percentile), respectively. Percentile values are from the PREDICT-HD population in this study.

Each outcome was standardised and cubic splines based on five knots (1st, 25th, 50th, 75th, and 99th percentiles) were used in the linear mixed-effects

regression portion to model non-linear change.[12–14,21] We fitted two joint models for each measure: a reduced model that provided information about the baseline prediction by a marker of the hazard for motor diagnosis (at a CAP of 290), and a full model that incorporated change of the marker in the prediction. A significant *g* estimate meant that a measure accounted for variability in the timing of diagnosis in addition to CAG expansion and age. The covariates in all models were sex and number of years in education. For cognitive measures, depression (Beck Depression Inventory) was added as a covariate to account for mood changes. For imaging measures, field strength was added as a covariate because some sites updated their scanners during the study. The hazard ratio (HR) was computed as exp(*g*) and served as the primary effect size (HR^{-1} was used when the *g* estimate was negative). A significant HR indicates that a measure adds to prediction beyond that of CAG and age (as indexed by CAP).

In a subsequent preplanned analysis, we characterised the risk of motor diagnosis over the lifespan of individuals with the gene mutation for Huntington's disease. We used individual fitted values from the linear mixed-effects regression spline model to obtain baseline values at a CAP of 290. We used the baseline information in a separate (ie, not joint) Cox model to predict time to diagnosis along with the covariates. We estimated the cumulative hazard on the basis of the fitted models for various baseline predictor values.

We also did a preplanned ancillary analysis to examine the natural history of key variables from the premanifest phase to diagnosis; all people who were diagnosed with Huntington's disease during the study with a DCL of 4 were used for this analysis. 206 control participants were used in a post-hoc analysis along with all 1078 gene-expanded participants examining the heterogeneity of the UHDRS total motor score (appendix). The time metric was years to diagnosis and we used cubic spline curves with linear mixed-effects regression models to allow for non-linear trends over time.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1078 individuals with a CAG expansion from the PREDICT-HD study whose data had been entered into the database by April, 2014, were included in this analysis (table 1, appendix). The study concluded in August, 2014. Participants were followed up for a mean of 5·1 years (SD 3·3; range 0·0–12·0). 959 (89%) participants had data for two or more years, and 118 (11%) had data for only one timepoint (appendix). 225 (21%) participants received a motor diagnosis during the study, as defined by the DCL. 260 control participants (with fewer than 36 CAG repeats) were included in an ancillary analysis to examine lower-bound cutoffs of total motor score based on normal ageing (appendix).

Figure 1 shows age at diagnosis as a function of CAG expansion for the converters who obtained a motor diagnosis during the study. The squared correlation (r^2) between CAG repeat length and age at Huntington's disease diagnosis was 0·53. Age at diagnosis can vary widely for individuals with the same CAG expansion—eg, for patients with 40 CAG repeats, the range for age at diagnosis ranges from 37·6 to 68·8 years, and the difference between the first and third quartile is 15 years. Mean CAP at motor diagnosis was 447, which for the sample CAG quartiles of 41 repeats, 42 repeats, and

	Participants not diagnosed with Huntington's disease during the study (n=853)	Participants diagnosed with Huntington's disease during the study (n=225)	Combined (n=1078)
Women	540 (63%)	147 (65%)	687 (64%)
Age (years)	38·92 (10·24)	43·03 (10·31)	39·78 (10·39)
Number of CAG repeats	42·21 (2·58)	43·57 (2·85)	42·49 (2·69)
CAP	334·89 (82·74)	436·59 (81·82)	356·12 (92·30)
Education (years)	14·56 (2·62)	14·08 (2·50)	14·46 (2·60)
Time in study (years)	4·28 (3·31)	6·66 (2·48)	4·78 (3·30)

Data are mean (SD) or n (%). CAG=cytosine-adenine-guanine. CAP=CAG-Age Product ([age in years at baseline] × [CAG-33·66]).

Table 1: **Baseline characteristics**

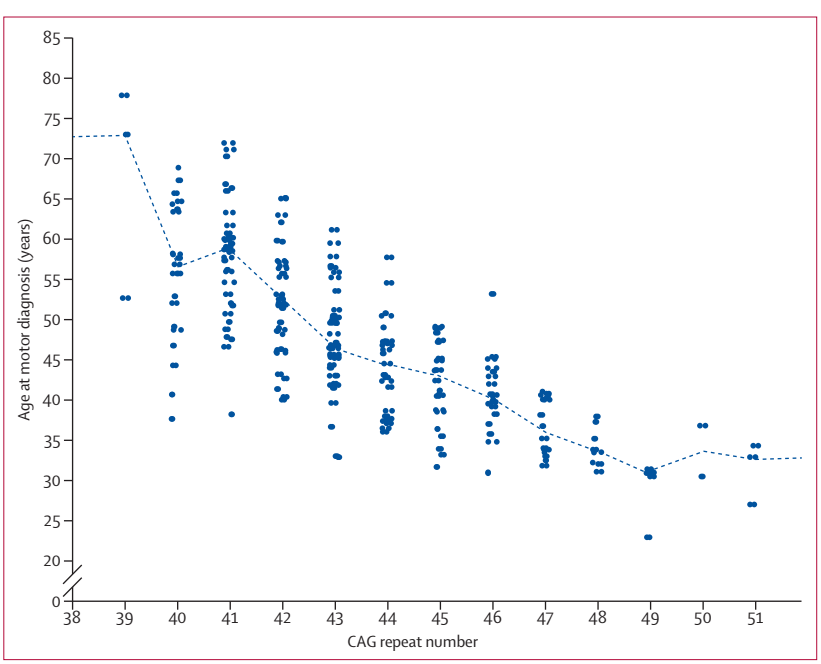

Figure 1: **Age at diagnosis by CAG repeat number for the 225 participants who received a motor diagnosis of Huntington's disease during the study**
The dashed line shows the median age of motor diagnosis for each cytosine-adenine-guanine (CAG) repeat number.

	Participants	Observations	Events	Cross-sectional prediction (reduced model)			Longitudinal prediction (full model)		
				g (SE)	*Z* value (p value)	HR or HR^{-1} (95% CI)	g (SE)	*Z* value (p value)	HR or HR^{-1} (95% CI)
Motor domain									
Total motor score	1073	3661	225	0·98 (0·16)	6·20 (<0·0001)	2·65 (1·95–3·61)	1·12 (0·16)	7·23 (<0·0001)	3·07 (2·26–4·16)
Chorea	1073	3661	225	1·09 (0·17)	6·53 (<0·0001)	2·99 (2·15–4·15)	1·16 (0·16)	7·08 (<0·0001)	3·19 (2·31–4·40)
Bradykinesia	1073	3661	225	0·76 (0·15)	5·05 (<0·0001)	2·14 (1·59–2·87)	0·89 (0·13)	6·80 (<0·0001)	2·44 (1·89–3·16)
Ocular	1073	3661	225	0·73 (0·19)	3·94 (<0·0001)	2·07 (1·44–2·98)	0·82 (0·20)	4·07 (<0·0001)	2·28 (1·53–3·39)
Rigidity	1073	3661	225	0·29 (0·18)	1·61 (0·1073)	1·33 (0·94–1·88)	0·36 (0·17)	2·17 (0·0298)	1·44 (1·04–2·00)
Dystonia	1073	3661	225	0·66 (0·25)	2·57 (0·0101)	1·93 (1·17–3·17)	NA	NA	NA
Imaging domain									
Putamen	980	1774	147	−1·11 (0·15)	−7·36 (<0·0001)	3·03 (2·25–4·06)	−1·20 (0·17)	−6·95 (<0·0001)	3·32 (2·37–4·65)
Hippocampus	980	1774	147	−0·58 (0·11)	−5·29 (<0·0001)	1·78 (1·44–2·21)	−0·64 (0·11)	−6·02 (<0·0001)	1·90 (1·54–2·35)
Lobar grey matter	967	1703	146	−0·59 (0·14)	−4·38 (<0·0001)	1·81 (1·39–2·36)	−0·75 (0·13)	−5·95 (<0·0001)	2·11 (1·65–2·69)
CSF	985	1785	148	0·38 (0·08)	4·87 (<0·0001)	1·47 (1·26–1·71)	0·48 (0·09)	5·50 (<0·0001)	1·62 (1·36–1·92)
Accumbens	980	1774	147	−0·87 (0·19)	−4·48(<0·0001)	2·39 (1·63–3·49)	−1·00 (0·18)	−5·48 (<0·0001)	2·71 (1·90–3·88)
Globus pallidus	980	1774	147	−1·11 (0·26)	−4·29 (<0·0001)	3·04 (1·83–5·04)	−1·29 (0·25)	−5·19 (<0·0001)	3·64 (2·23–5·92)
Caudate	980	1774	147	−0·73 (0·18)	−4·11 (<0·0001)	2·07 (1·46–2·92)	−0·85 (0·18)	−4·84 (<0·0001)	2·34 (1·66–3·29)
Thalamus	980	1774	147	−0·34 (0·14)	−2·49 (0·0129)	1·40 (1·07–1·84)	−0·35 (0·14)	−2·60 (0·0093)	1·42 (1·09–1·85)
Lobar white matter	952	1659	143	−0·09 (0·08)	−1·08 (0·2795)	1·09 (0·93–1·29)	−0·12 (0·07)	−1·67 (0·0946)	1·13 (0·98–1·31)
Cognitive domain									
Stroop word	979	2879	178	−0·75 (0·11)	−7·13 (<0·0001)	2·12 (1·72–2·61)	−0·84 (0·11)	−7·79 (<0·0001)	2·32 (1·88–2·87)
Smell ID	962	2139	159	−0·45 (0·08)	−5·59 (<0·0001)	1·57 (1·34–1·83)	−0·54 (0·08)	−6·87 (<0·0001)	1·72 (1·47–2·00)
SDMT	979	2876	178	−0·68 (0·12)	−5·84 (<0·0001)	1·97 (1·57–2·48)	−0·72 (0·12)	−6·20 (<0·0001)	2·05 (1·63–2·57)
Stroop colour	979	2877	178	−0·73 (0·15)	−4·98 (<0·0001)	2·09 (1·56–2·78)	−0·81 (0·13)	−6·15 (<0·0001)	2·25 (1·74–2·91)
Stroop interference	979	2869	178	−0·76 (0·15)	−4·89 (<0·0001)	2·13 (1·57–2·89)	−0·77 (0·13)	−5·88 (<0·0001)	2·17 (1·68–2·81)
Time production	759	1391	104	0·44 (0·12)	3·58 (0·0003)	1·55 (1·22–1·97)	0·59 (0·11)	5·43 (<0·0001)	1·81 (1·46–2·23)
Speeded tapping	764	1392	104	0·38 (0·10)	3·67 (0·0002)	1·47 (1·20–1·80)	0·46 (0·09)	4·86 (<0·0001)	1·58 (1·32–1·91)
Emotional recognition	765	1406	103	−0·42 (0·14)	−2·99 (0·0028)	1·52 (1·15–1·99)	−0·52 (0·14)	−3·73 (0·0002)	1·68 (1·28–2·21)
Trail Making Test (part A)	974	2217	167	0·18 (0·07)	2·50 (0·0124)	1·20 (1·04–1·38)	0·21 (0·08)	2·55 (0·0109)	1·24 (1·05–1·45)
Trail Making Test (part B)	970	2197	165	0·16 (0·09)	1·89 (0·0592)	1·18 (0·99–1·40)	NA	NA	NA
Psychiatric domain									
FrSBe executive subscale	1002	3071	191	0·53 (0·09)	5·77 (<0·0001)	1·69 (1·42–2·03)	0·62 (0·09)	6·64 (<0·0001)	1·86 (1·55–2·23)
SCL-90 O-C	1009	3120	195	0·56 (0·10)	5·34 (<0·0001)	1·75 (1·42–2·15)	0·64 (0·11)	5·93 (<0·0001)	1·90 (1·54–2·35)
FrSBe apathy subscale	1002	3071	191	0·37 (0·08)	4·53 (<0·0001)	1·45 (1·23–1·70)	0·46 (0·08)	5·37 (<0·0001)	1·58 (1·34–1·86)
SCL-90 GSI	988	2943	184	0·46 (0·09)	4·89 (<0·0001)	1·58 (1·32–1·90)	0·51 (0·10)	5·34 (<0·0001)	1·67 (1·38–2·02)
FrSBe disinhibition subscale	1002	3071	191	0·36 (0·09)	3·84 (0·0001)	1·43 (1·19–1·72)	0·42 (0·09)	4·56 (<0·0001)	1·52 (1·27–1·81)
SCL-90 hostility subscale	1009	3120	195	0·35 (0·11)	3·35 (0·0008)	1·42 (1·16–1·75)	0·35 (0·10)	3·38 (0·0007)	1·42 (1·16–1·75)
SCL-90 depression subscale	987	2942	184	0·45 (0·12)	3·75 (0·0002)	1·57 (1·24–1·99)	NA	NA	NA
SCL-90 anxiety subscale	988	2943	184	0·39 (0·10)	3·94 (<0·0001)	1·48 (1·22–1·80)	NA	NA	NA
BDI	816	2297	137	0·25 (0·10)	2·43 (0·0149)	1·28 (1·05–1·56)	NA	NA	NA
Functional domain									
Total functional capacity	1071	3626	225	−0·53 (0·10)	−5·15 (<0·0001)	1·70 (1·39–2·08)	−0·61 (0·10)	−6·34 (<0·0001)	1·84 (1·52–2·22)
Functional activity scale	827	2326	137	−0·36 (0·11)	−3·39 (0·0007)	1·43 (1·16–1·76)	−0·40 (0·10)	−3·90 (<0·0001)	1·49 (1·22–1·83)
ECog-C	602	911	101	0·37 (0·13)	2·76 (0·0058)	1·44 (1·11–1·87)	0·43 (0·13)	3·22 (0·0013)	1·54 (1·18–2·00)
WHODAS-C	529	736	67	0·48 (0·21)	2·25 (0·0245)	1·61 (1·06–2·44)	NA	NA	NA
ECog-P	678	1093	120	0·45 (0·09)	5·12 (<0·0001)	1·57 (1·32–1·86)	NA	NA	NA
WHODAS-P	581	850	63	0·42 (0·14)	3·11 (0·0019)	1·53 (1·17–1·99)	NA	NA	NA

Within each domain, measures are ranked by absolute *Z* value for the association parameter (g) of the full model. Events are the number of conversions to motor diagnosis. Hazard ratio (HR) or inverse hazard ratio (HR^{-1}) show the hazard for motor diagnosis associated with a difference of one SD in each measure. All measures in the imaging domain were corrected for intracranial volume. NA=not available, because full model could not be estimated because of absence or low variability in the individual rate of change over time. Smell ID=University of Pennsylvania Smell Identification Test. SDMT=Symbol Digit Modalities Test. FrSBe=Frontal Systems Behavioral Scale. SCL-90= Symptom Checklist 90. O-C=obsessive-compulsive. GSI=Global Severity Index. BDI=Beck Depression Inventory. ECog-C=Everyday Cognition rating scale, companion rating. WHODAS-C=WHO Disability Assessment Schedule, companion rating. ECog-P=Everyday Cognition rating scale, participant rating. WHODAS-P=WHO Disability Assessment Schedule, participant rating.

Table 2: **Prediction of risk of a motor diagnosis of Huntington's disease: joint modelling results**

44 repeats represents the rounded ages of 61, 54, and 43 years, respectively.

Table 2 shows the joint modelling results (each measure was tested separately). The longitudinal variables are sorted within each domain on the basis of the absolute *Z* value of *g* from the full model. The column for reduced-model *g* estimates shows that the baseline information was a significant predictor of the hazard of motor diagnosis for 37 of 40 measures. A comparison shows that the full-model *g* estimates were larger than the reduced model estimates in absolute value for every measure for which a full-model estimate could be made. Thus, prediction of motor diagnosis based on baseline information and longitudinal change information was stronger than prediction based only on baseline information.

Based on the results for the full model, the largest effect size in the motor domain was for total motor score (table 2). For the imaging domain, putamen volume was the strongest predictor, and the strongest cognitive-domain predictor was the Stroop word score. The best psychiatric-domain predictor was executive functioning, and total functional capacity was the strongest functional measure (table 2).

Figure 2 shows the cumulative hazard (accumulated risk rate) as a function of CAP for putamen volume, total motor score, and Stroop word test. These measures were the strongest predictors within the three strongest domains (functional and psychiatric measures, although significant, had weaker prediction in terms of the estimated HRs; table 2). The no-predictor model represents the cumulative hazard associated with only CAG expansion and age (both variables are indexed by CAP). The baseline was set to a CAP of 290, and the predictor curves were generated for values of the variables representing no deterioration and advanced deterioration. The no-deterioration values (total motor score 0, ratio of putamen volume to intracranial volume 0·008, and Stroop word score 183) were the most extreme values in the sample (minimum for total motor score, and maximum for the others). The advanced-deterioration values (total motor score 15, ratio of putamen volume to intracranial volume 0·0038, Stroop word score 85) were the medians for participants in the sample with a DCL of 3. When there is advanced deterioration at baseline, the cumulative hazard for the predictors increases at a faster rate than when the covariates are ignored or there is no deterioration. Conversely, when there is no deterioration at baseline, the cumulative hazard for the predictors increases at a slower rate than when the covariates are ignored.

Figure 3 shows individual empirical curves and fitted spline curves for the participants who received a motor diagnosis during the study, for the two strongest predictors in each domain (based on absolute *Z* values). Descriptive information about all the variables for these participants at study entry and time of diagnosis is provided in the appendix.

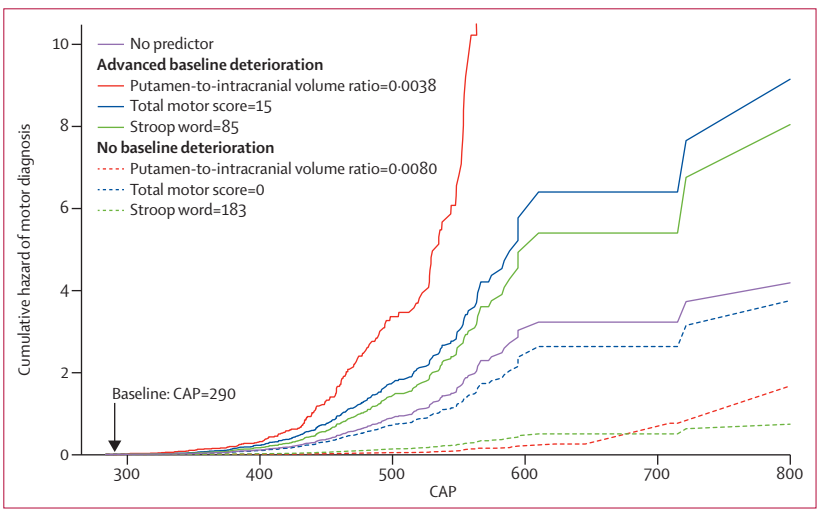

Figure 2: **Cumulative hazard (accumulated risk rate) of motor diagnosis by CAP for various baseline predictor values**

The solid black line denotes the cumulative hazard for a model with no predictor, representing prediction based on only cytosine-adenine-guanine (CAG) expansion and age, as summarised by CAG-Age Product (CAP; [age in years at baseline] × [CAG–33·66]). Putamen volume is corrected for intracranial volume. As a reference, a CAP of 290 corresponds to age 31 years and a CAP of 600 corresponds to age 64 years for an individual with a 43 CAG repeats (the 75th sample percentile).

Discussion

Our results show that several clinical and biological measures can improve the prediction of Huntington's disease diagnosis beyond that obtained by CAG repeat length and age alone. The strongest predictors (in terms of absolute *Z* values) were in the motor (total motor score), imaging (putamen volume), and cognitive (Stroop word test) domains. Psychiatric and functional measures were significant, but relatively weak, predictors of manifest Huntington's disease. These findings suggest that models for the prediction of Huntington's disease onset can be substantially improved by use of straightforward clinical (motor and cognitive) assessments (panel). Volumetric MRI measures can also be used as predictors.

Because CAP is age adjusted for CAG repeat number, the cumulative risk of diagnosis increases as CAP increases because the likelihood of motor diagnosis increases as people age. As a result, the no-predictor curve in figure 2 represents the accumulated risk rate that could be predicted on the basis of only CAG and age (and their interaction). When a predictor is taken into account, the risk profile is modified on the basis of the predictor value at baseline. The modification can result in a very different risk profile compared with CAP alone. For people with advanced deterioration at baseline, the risk of motor diagnosis is estimated to be greater when a predictor is used, whereas for people with no or little deterioration, the risk is less than that predicted by CAG and age alone. Thus, a clinical predictor is informative for risk assessment for future motor diagnosis beyond the information provided by CAG and age. Further research is needed to detect additional genetic, environmental, and biological

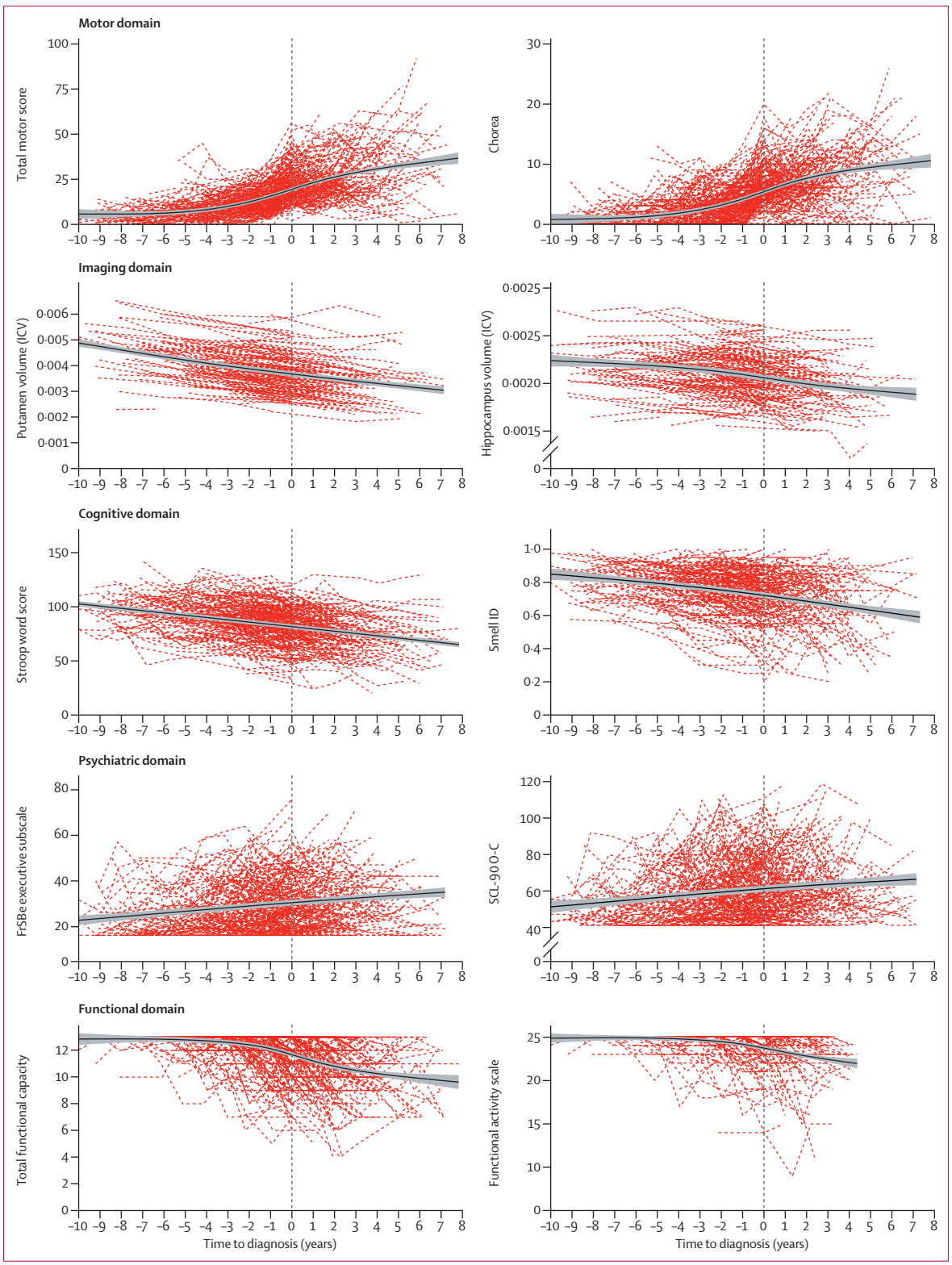

Figure 3: **Trajectories of motor, imaging, cognitive, psychiatric, and functional measures for the 225 participants who received a motor diagnosis of Huntington's disease during the study**

The top two strongest predictors in each domain are shown. Dashed lines are individual empirical data and solid lines are cubic spline curves (shading shows 95% CIs). The vertical line in each panel denotes year of diagnosis (set to year 0). ICV=intracranial-corrected volume. Smell ID=University of Pennsylvania Smell Identification Test. FrSBe=Frontal Systems Behavior Scale. SCL-90 O-C=Symptom Checklist 90 (obsessive-compulsive).

predictors of motor diagnosis, since predictors of disease onset might also lead to new avenues for intervention.

In a follow-up analysis, we assessed a composite of total motor score, putamen volume, and Stroop word test, but use of the composite did not improve prediction compared with the individual measures (data not shown). A complication of our cumulative hazard results is that the maximum Stroop word scores might not represent the absence of deterioration, but rather an advanced education level or high intelligence. The converse also holds for low Stroop word scores. However, the association identified remains valid: superior or inferior Stroop word test performance at baseline affects the future estimate of risk. Similar considerations are also relevant for putamen volume and total motor score.

The best motor predictor of Huntington's disease diagnosis was total motor score, which is unsurprising since diagnosis is based on motor findings. This finding emphasises the value of the motor examination, even in the premanifest period. It is consistent with previous findings of subtle motor abnormalities years before diagnosis, which can accelerate just before diagnosis.[6,22] Subdomains for chorea, bradykinesia, and oculomotor abnormalities were also predictive.

The strongest predictive cognitive measure was the Stroop word test, a timed reading task. Previously, we documented 19 cognitive tasks that showed significant longitudinal change before motor diagnosis.[12] Our results suggest that performance on just one of the most robust of these tests can significantly improve diagnostic prediction. The most robust cognitive tests take just a few minutes to do and can be used in various settings, making them valuable for design of future studies and clinical practice.

The usefulness of brain imaging markers in the detection of Huntington's disease has been documented in several studies over the past decade.[2,23,24] Striatal volume consistently distinguishes people with the *HTT* disease mutation from those without and tracks disease progression.[12] Our results show that imaging measures were among the best predictors of diagnosis in premanifest Huntington's disease, and their pre-eminence in this study offers biological validity for the models presented (ie, Stroop and total motor score have biological validity since they are associated with volume loss on MRI, which is a characteristic of Huntington's disease). The use of imaging measures might translate into advances in clinical trial design, with respect to both selection criteria and outcome measures. Imaging might also be useful in clinical care and education, although broad dissemination of imaging predictors would necessitate standardisation of image acquisition and analysis protocols for clinical care.

Our findings validate and extend results from other studies that used smaller samples, shorter follow-up, and varying endpoints.[2–11] Overall, strong evidence now exists that cognitive, motor, and imaging deficits are evident before traditional motor diagnosis and might provide an opportunity for earlier intervention, treatment, and support. The predictive usefulness of the markers suggested by our results can be integrated into clinical trial design and be used to advance clinical care through refined diagnostic and prognostic guidelines.

Much evidence exists that the diagnosis of Huntington's disease is made fairly late in the disease course, after a high proportion of people already show substantial cognitive decline,[13,25] psychiatric abnormalities,[26–28] and motor impairment,[6,22] and at a time when, on average, more than half of their striatal volume is lost.[2] Notably, many people are diagnosed after major changes in functioning have occurred (eg, loss of usual employment or ability to drive) and after a reduction in basic activities of daily living (requiring financial or care assistance).[29–32] An earlier diagnosis might be beneficial with respect to potential future therapeutic interventions and life planning.[33,34]

Our data suggest some interesting models for the course of Huntington's disease. Based on what is to our knowledge the largest sample of prospectively followed people who converted to Huntington's disease, our results suggest that many of the clinical markers of

***Panel:* Research in context**

Systematic review

We searched PubMed and Medline for articles published in English up to Aug 25, 2014, using the search terms "Huntington disease", "longitudinal", "prospective", "onset", and "diagnosis". We restricted our search to reports of studies of human participants aged 19 years or older. We also reviewed the reference lists of identified articles. Since no previous publications from the PREDICT-HD study had examined comprehensive prediction of diagnosis, all such reports were excluded. We identified seven reports[3,5,7–11] of studies in which prospective data were used to predict Huntington's disease diagnosis on the basis of motor criteria. Sample sizes for participants prospectively diagnosed were 21–70 and length of follow-up varied from 2·5 to 5 years. Four[3,8–10] of the seven studies identified investigated only cognitive predictors, one study[7] investigated only dietary predictors, and the remaining two studies[5,11] examined various comprehensive predictors of prospective diagnosis. Studies showed that cognitive tests of executive control, subtle motor abnormalities, brain imaging, and subjective complaints were predictive of Huntington's disease diagnosis. Using data from the Huntington Study Group, Langbehn and Paulsen[5] showed cognitive measures, motor measures, and self-reported symptoms to be predictive of traditional motor diagnosis (ie, a rating of 4 on the Unified Huntington's Disease Rating Scale). Although Tabrizi and colleagues[11] did not examine traditional motor criteria for diagnosis, their findings suggest that cognitive measures, quantitative motor measures, and imaging measures are predictive of motor onset.

Interpretation

Our study is the first to use comprehensive longitudinal assessments to prospectively predict traditional motor diagnosis in Huntington's disease. Joint modelling of longitudinal change and time to Huntington's disease diagnosis identified several significant phenotypic and biological predictors (eg, imaging) that might be useful as endpoints in clinical trials and for participant selection. These findings fill a gap in the scientific literature by identifying predictors of Huntington's disease diagnosis in addition to CAG expansion and age. Our results provide insights into the nature of Huntington's disease progression and show that brief clinical assessments have the potential to enhance prediction of motor diagnosis.

disease progression (ie, cognitive, sensory, and psychiatric variables) progress in a near linear fashion and decline in concert with biological markers of brain imaging abnormalities. Additionally, they suggest that motor and functional variables progress in a non-linear way, which is reflected by the fact that motor signs and functional impairment become evident only at specific points of disease progression. Several possible explanations could account for the variations in disease progression. One explanation might be that atrophy of each individual brain region proceeds fairly linearly, beginning with the striatum, but as additional brain regions undergo degeneration and dysfunction, their combined effect causes acceleration of the clinical expression of disease. An alternative hypothesis is that, at some point, a threshold of brain volume is surpassed, triggering acceleration of motor and functional deficits. Researchers making the crucial choice of outcome measures for clinical trials might benefit from our findings, such that studies can be better designed to improve the possibility of documenting therapeutic effects, should they occur. In view of the variation in motor and functional changes across the disease course, selection of participants at varying disease stages could drastically change interpretations made about the effects of an intervention.

Some qualifications should be taken into account in the interpretation of these research findings. The baseline for prediction was defined at a disease burden score at which it is known that the PREDICT-HD sample has the earliest detectable change in motor signs.[6] Should other samples suggest the examination of other CAP scores as baseline in the premanifest period, the estimates could vary accordingly. Encouragingly, however, our findings are similar to those reported from studies of smaller samples followed up for shorter durations.[11] Replication in other samples will continue to refine the predictive models used. Translation of these models into clinical care will require further research to determine how such information can be integrated into genetic counselling. Advances in diagnosis and prognosis will depend on clinical consensus and guidelines. Implementation of new diagnostic and prognostic criteria will necessitate patient-centred clinical outcome research to document best practices for families affected by Huntington's disease who choose to obtain greater prognostic information than they do at present.

Additional caveats concern the variability noted in this study. Individual values for the predictive measures assessed varied widely, especially for total motor score. Individuals might have had different motor examiners over time, which could inflate the variability of the total motor score. Early in the study, substantial variation in total motor score was noted and efforts were made to assure data integrity (appendix). Another source of heterogeneity was introduced by the upgrading of MRI scanners at all sites (from 1·5T to 3T). However, we adjusted for scanner strength, both in the image processing and in the statistical analysis (appendix). Despite the substantial variability, both the total motor score and the imaging measures were among the strongest predictors. Thus, potential sources of variance such as different raters and scanners did not outweigh the predictive power of the measures. Future studies that constrain sources of variance by having the same scanners or the same people assessing motor function might show even larger effect sizes than those reported here.

The detection and tracking of early clinical signs and symptoms in Huntington's disease is crucial to choosing outcome measures useful for clinical trials. Treatments that affect symptoms of disability in motor, cognitive, psychiatric, and functional domains can be essential components of clinical trials and are often mandated by regulatory agencies. The outcome measures reported here might have value in the selection of research participants and might help researchers to choose outcomes that are associated with a meaningful endpoint—that of being diagnosed.

Contributors

JSP, CAR, CJE, HJJ, and EHA contributed to study design. JSP, CJE, JKW, HJJ, EHA, HJB, and RAB participated in data collection. JSP, JDL, HJJ, EHA, YZ, and HJB did the data analysis. JSP, CAR, DLH, JKW, HJJ, EHA, YZ, and HJB contributed to data interpretation. HJB contributed to data integration. JSP, JDL, CAR, JKW, HJW, and YZ wrote the report. JSP, JDL, DLH, HJW, HJJ, EHA, YZ, HJB, and RAB edited the report for important intellectual content. JDL created figures and tables and JSP searched the scientific literature. CJE provided analysis and interpretation for appropriate ethical content and handling of confidential or sensitive information. HJW oversaw data quality control and training of the neuropsychological assessment research core. JSP provided study supervision and obtained funding for the study.

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Declaration of interests

JSP has served on an advisory board for Lundbeck and has a consulting agreement with ProPhase. JDL, CAR, DLH, CJE, JKW, HJW, HJJ, EHA, YZ, HJB, and RAB declare no competing interests.

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References

1 Andrew SE, Goldberg YP, Kremer B, et al. The relationship between trinucleotide (CAG) repeat length and clinical features of Huntington's disease. *Nat Genet* 1993; **4:** 398–403.

2 Aylward EH, Liu D, Nopoulos PC, et al. Striatal volume contributes to the prediction of onset of Huntington disease in incident cases. *Biol Psychiatry* 2012; **71:** 822–28.

3 Brandt J, Inscore AB, Ward J, et al. Neuropsychological deficits in Huntington's disease gene carriers and correlates of early "conversion". *J Neuropsychiatry Clin Neurosci* 2008; **20:** 466–72.

4 Harrington DL, Smith MM, Zhang Y, Carlozzi NE, Paulsen JS, PREDICT-HD Investigators of the Huntington Study Group. Cognitive domains that predict time to diagnosis in prodromal Huntington disease. *J Neurol Neurosurg Psychiatry* 2012; **83:** 612–19.

5 Langbehn DR, Paulsen JS, Huntington Study Group. Predictors of diagnosis in Huntington disease. *Neurology* 2007; **68:** 1710–17.

6 Long JD, Paulsen JS, Marder K, et al. Tracking motor impairments in the progression of Huntington's disease. *Mov Disord* 2014; **29:** 311–19.

7 Marder K, Gu Y, Eberly S, et al. Relationship of Mediterranean diet and caloric intake to phenoconversion in Huntington disease. *JAMA Neurol* 2013; **70:** 1382–88.

8 Paulsen JS, Zhao H, Stout JC, et al. Clinical markers of early disease in persons near onset of Huntington's disease. *Neurology* 2001; **57:** 658–62.

9 Snowden JS, Craufurd D, Thompson J, Neary D. Psychomotor, executive, and memory function in preclinical Huntington's disease. *J Clin Exp Neuropsychol* 2002; **24:** 133–45.

10 Solomon AC, Stout JC, Weaver M, et al. Ten-year rate of longitudinal change in neurocognitive and motor function in prediagnosis Huntington disease. *Mov Disord* 2008; **23:** 1830–36.

11 Tabrizi SJ, Scahill RI, Owen G, et al. Predictors of phenotypic progression and disease onset in premanifest and early-stage Huntington's disease in the TRACK-HD study: analysis of 36-month observational data. *Lancet Neurol* 2013; **12:** 637–49.

12 Paulsen JS, Long JD, Johnson HJ, et al. Clinical and biomarker changes in premanifest Huntington disease show trial feasibility: a decade of the PREDICT-HD study. *Front Aging Neurosci* 2014; **6:** 78.

13 Paulsen JS, Smith MM, Long JD, PREDICT-HD investigators, coordinators of the Huntington Study Group. Cognitive decline in prodromal Huntington disease: implications for clinical trials. *J Neurol Neurosurg Psychiatry* 2013; **84:** 1233–39.

14 Paulsen JS, Hayden M, Stout JC, et al. Preparing for preventive clinical trials: the Predict-HD study. *Arch Neurol* 2006; **63:** 883–90.

15 Diggle PJ, Sousa I, Chetwynd AG. Joint modelling of repeated measurements and time-to-event outcomes: the fourth Armitage lecture. *Stat Med* 2008; **27:** 2981–98.

16 Wulfsohn MS, Tsiatis AA. A joint model for survival and longitudinal data measured with error. *Biometrics* 1997; **53:** 330–39.

17 Zhang Y, Long JD, Mills JA, et al. Indexing disease progression at study entry with individuals at-risk for Huntington disease. *Am J Med Genet B Neuropsychiatr Genet* 2011; **156B:** 751–63.

18 Langbehn DR, Hayden MR, Paulsen JS. CAG-repeat length and the age of onset in Huntington disease (HD): A review and validation study of statistical approaches. *Am J Med Genet B Neuropsychiatr Genet* 2010; **153B:** 397–408.

19 Penney JB Jr, Vonsattel JP, MacDonald ME, Gusella JF, Myers RH. CAG repeat number governs the development rate of pathology in Huntington's disease. *Ann Neurol* 1997; **41:** 689–92.

20 Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. *Nat Rev Neurol* 2014; **10:** 204–16.

21 Paulsen JS, Langbehn DR, Stout JC, et al. Detection of Huntington's disease decades before diagnosis: the Predict-HD study. *J Neurol Neurosurg Psychiatry* 2008; **79:** 874–80.

22 Biglan KM, Ross CA, Langbehn DR, et al. Motor abnormalities in premanifest persons with Huntington's disease: the PREDICT-HD study. *Mov Disord* 2009; **24:** 1763–72.

23 Bohanna I, Georgiou-Karistianis N, Hannan AJ, Egan GF. Magnetic resonance imaging as an approach towards identifying neuropathological biomarkers for Huntington's disease. *Brain Res Rev* 2008; **58:** 209–25.

24 Kloppel S, Henley SM, Hobbs NZ, et al. Magnetic resonance imaging of Huntington's disease: preparing for clinical trials. *Neuroscience* 2009; **164:** 205–19.

25 Duff K, Paulsen J, Mills J, et al. Mild cognitive impairment in prediagnosed Huntington disease. *Neurology* 2010; **75:** 500–07.

26 Beglinger LJ, Paulsen JS, Watson DB, et al. Obsessive and compulsive symptoms in prediagnosed Huntington's disease. *J Clin Psychiatry* 2008; **69:** 1758–65.

27 Duff K, Paulsen JS, Beglinger LJ, Langbehn DR, Stout JC, Predict-HD Investigators of the Huntington Study Group. Psychiatric symptoms in Huntington's disease before diagnosis: the Predict-HD study. *Biol Psychiatry* 2007; **62:** 1341–46.

28 Epping EA, Mills JA, Beglinger LJ, et al. Characterization of depression in prodromal Huntington disease in the neurobiological predictors of HD (PREDICT-HD) study. *J Psychiatr Res* 2013; **47:** 1423–31.

29 Beglinger LJ, O'Rourke JJ, Wang C, et al. Earliest functional declines in Huntington disease. *Psychiatry Res* 2010; **178:** 414–18.

30 Downing NR, Kim JI, Williams JK, et al. WHODAS 2.0 in prodromal Huntington disease: measures of functioning in neuropsychiatric disease. *Eur J Hum Genet* 2014; **22:** 958–63.

31 Williams J, Downing N, Vaccarino AL, Guttman M, Paulsen JS. Self reports of day-to-day function in a small cohort of people with prodromal and early HD. *PLoS Curr* 2011; **3:** RRN1254.

32 Paulsen JS, Wang C, Duff K, et al. Challenges assessing clinical endpoints in early Huntington disease. *Mov Disord* 2010; **25:** 2595–603.

33 Rothstein M, Siegal G. Health information technology and physicians' duty to notify patients of new medical developments. *Hous J Health L & Policy* 2012; **12:** 93–136.

34 Williams JK, Erwin C, Juhl A, et al. Personal factors associated with reported benefits of Huntington disease family history or genetic testing. *Genet Test Mol Biomarkers* 2010; **14:** 629–36.