VIEWPOINT

Diagnostic Criteria for Huntington's Disease Based on Natural History

Ralf Reilmann, MD,[1,2*] Blair R. Leavitt, MD, CM,[3] and Christopher A. Ross, MD[4*]

[1]George-Huntington-Institute, Technology-Park, Muenster, Germany
[2]Department of Neurodegenerative Diseases and Hertie-Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany
[3]Centre for Molecular Medicine and Therapeutics, and Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada
[4]Division of Neurobiology, Department of Psychiatry, and Departments of Neurology, Neuroscience, and Pharmacology, and Program in Cellular and Molecular Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

ABSTRACT: Huntington's disease (HD) is currently diagnosed based on the presence of motor signs indicating 99% "diagnostic confidence" for HD. Recent advances in the understanding of HD natural history and neurobiology indicate that disease-related brain changes begin at least 12 to 15 years before the formal diagnosis based on motor onset. Furthermore, subtle motor dysfunction, cognitive changes, and behavioral alterations are often seen before diagnosis made according to the current criteria. As disease-modifying treatments are developed, likely beginning therapy early will be desirable. We therefore suggest that expanded diagnostic criteria for HD should be adapted to better reflect the natural history of the disease, to enable the conduct of clinical trials in premanifest subjects targeting prevention of neurodegeneration, and to facilitate earlier symptomatic treatment. We propose a new set of criteria for HD diagnostic categories in the International Classification of Diseases that reflect our current understanding of HD natural history and pathogenesis. Based on defined criteria, for example, the Diagnostic Confidence Level and the Total Functional Capacity scales of the Unified Huntington's Disease Rating Scale, HD should be divided in the categories "genetically confirmed" with the subcategories "presymptomatic," "prodromal," and "manifest" and "not genetically confirmed" subdivided into "clinically at risk," "clinically prodromal," and "clinically manifest." © 2014 International Parkinson and Movement Disorder Society

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According to currently accepted criteria, Huntington's disease (HD) is formally diagnosed in a person who 1) carries a known CAG-expanded allele of the HD gene or has a family history of HD and 2) develops motor symptoms that are "unequivocal signs of HD" as defined in the "Diagnostic Confidence Level" (DCL) of the Unified Huntington's Disease Rating Scale (UHDRS). The DCL offers the following levels of confidence: 0 = normal (no motor abnormalities); 1 = nonspecific motor abnormalities; 2 = motor abnormalities that may be signs of HD (50–89% confidence); 3 = motor abnormalities that are likely signs of HD (90–98% confidence); 4 = motor abnormalities that are unequivocal signs of HD (≥99% confidence).[1] Within the UHDRS, motor symptoms are assessed using the Total Motor Score (TMS),[2] which is a well-established assessment tool in clinical research and is frequently used as an endpoint in clinical trials. The DCL assesses the clinician's confidence that, based on the TMS examination, the motor signs unequivocally represent HD, in other words, an otherwise unexplained extrapyramidal movement disorder with, for example, chorea, dystonia, bradykinesia, or rigidity. Only a person who receives a score of 4 on the DCL for the first time is said to have experienced "motor

*Correspondence to: Dr. Ralf Reilmann, MD, Founding Director, George-Huntington-Institute, Technology Park Muenster, Johann-Krane Weg 27, 48149 Muenster, Email: ralf.reilmann@ghi-muenster.de; or Dr. Christopher A. Ross, MD, PhD, Professor of Psychiatry, Neurology, Pharmacology and Neuroscience, Director, Division of Neurobiology, Director, Baltimore Huntington's Disease Center, Johns Hopkins University School of Medicine, CMSC 8-121, 600 North Wolfe Street, Baltimore, MD 21287, USA, E-mail: caross@jhu.edu

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onset," and this is the formal confirmation of the HD diagnosis as defined for research purposes today.

The current version of the UHDRS also asks for a DCL rating that expands to nonmotor features: "Based on the entire UHDRS, which besides the TMS offers assessments for cognitive, behavioral, and functional components,[2] do you believe with a confidence level ≥99% that this participant has manifest HD?"[3] Of note, this still does not include history. An expanded and more clinically relevant question could ask, "Based on the entire UHDRS (motor, cognitive, behavioral, and functional components), *and all available history* do you believe with a confidence level ≥99% that this participant has manifest HD?"

Several multi-site natural history and biomarker studies have recently significantly extended our knowledge about the neurobiology of HD, particularly 1) PREDICT-HD, with a total of about 800 premanifest HD cases and 200 control individuals, studied for up to 10 years[3-5]; and 2) TRACK-HD, having studied 360 individuals (240 CAG expansion positive, of which half were premanifest, and 120 matched controls), with extensive annual assessments involving imaging and objective and clinical measures for 3 years.[6-9]

In both PREDICT-HD and TRACK-HD subtle clinical motor abnormalities, cognitive changes, and often behavioral alterations occurred before the point when motor onset can be diagnosed according to current criteria.[3,6] Selective regional brain atrophy begins at least 12 to 15 years before the point at which manifest HD can be diagnosed[6,10] and exhibits measurable progression even early on,[7-9,11,12] confirming earlier single-site data.[13] These changes in brain volume are accompanied by changes in motor physiology as assessed by sensitive quantitative motor (Q-Motor) measures early on, suggesting a link between changes in brain structure and neuronal function.[14-17] Cognitive and behavioral deficits also commonly occur within the decade before the current diagnosis.[9,18,19]

Thus, fairly good agreement exists regarding the natural history of HD, comprising early changes as described in more detail in our recent review.[20] The course of HD can be divided into "premanifest" and "manifest" periods (Fig. 1). The premanifest period can be further subdivided. Initially, a period occurs in which individuals show no subjective symptoms, measurable abnormalities, or clinical signs and are therefore termed "presymptomatic," usually up to 10 to 15 years before onset. Individuals may then enter the "prodromal" period, during which the gradual appearance of subtle motor, cognitive, and behavioral changes, which do not meet the current criteria for formal HD diagnosis based on motor onset, occurs.

Early detection and management of motor, behavioral and psychiatric problems may prolong functioning at work, increase social integration, and foster independence. Earlier diagnoses will facilitate design of clinical trials and, ultimately, the development of therapies targeting the prevention of neurodegeneration, or disease-modifying therapeutics.

We therefore propose new diagnostic categories for HD based on an improved understanding of natural history and provide more precise criteria to terms familiar in the field, such as "presymptomatic," "prodromal," and "manifest" HD. With reference to the current version of the "International Classification of Diseases" [ICD-10-GM-2014] published by the World Health Organization (http://apps.who.int/classifications/icd10/browse/2010/en#/G10), we propose new categories and subcategories for HD, based on the currently assigned code "G10" (Table 1). Although a definitive diagnosis of HD should be reserved for proven CAG expansion carriers, those developing symptoms and opting not to be tested genetically may be categorized as "clinically diagnosed" but "genetically not proven." In contrast, those with proven CAG expansion could be categorized as "genetically confirmed" HD.

Proposal for Diagnostic Criteria and Categories Based on Natural History of HD

The diagnosis of genetically confirmed HD is based on a CAG expansion of 36 or more repeats in the *Huntingtin* (*HTT*) gene.[21] All untested patients are categorized as "not genetically confirmed" (see later discussion and Table 1).

Huntington's Disease—Genetically Confirmed (G10.1)

We propose three categories for those diagnosed with "genetically confirmed" HD based on the following criteria to be specified in the International Classification of Diseases:

Huntington's Disease—Genetically Confirmed—Presymptomatic (G10.1.1)

In the presymptomatic diagnostic category, individuals do not exhibit symptoms and have no changes in function. Thus, no relevant changes are seen in the TMS of the UHDRS. For some individuals the TMS may have nonspecific points, presumed by the clinician to represent baseline. Thus, the DCL should be 0 or 1. No HD-related functional changes should be present. Imaging studies may show changes in brain structure, and quantitative motor assessments may show subtle deficits,[9,14] but no clinical correlates or functional impairment should be evident at this stage. Future studies may establish that other biomarkers such as mutant huntingtin (Htt) concentration in peripheral

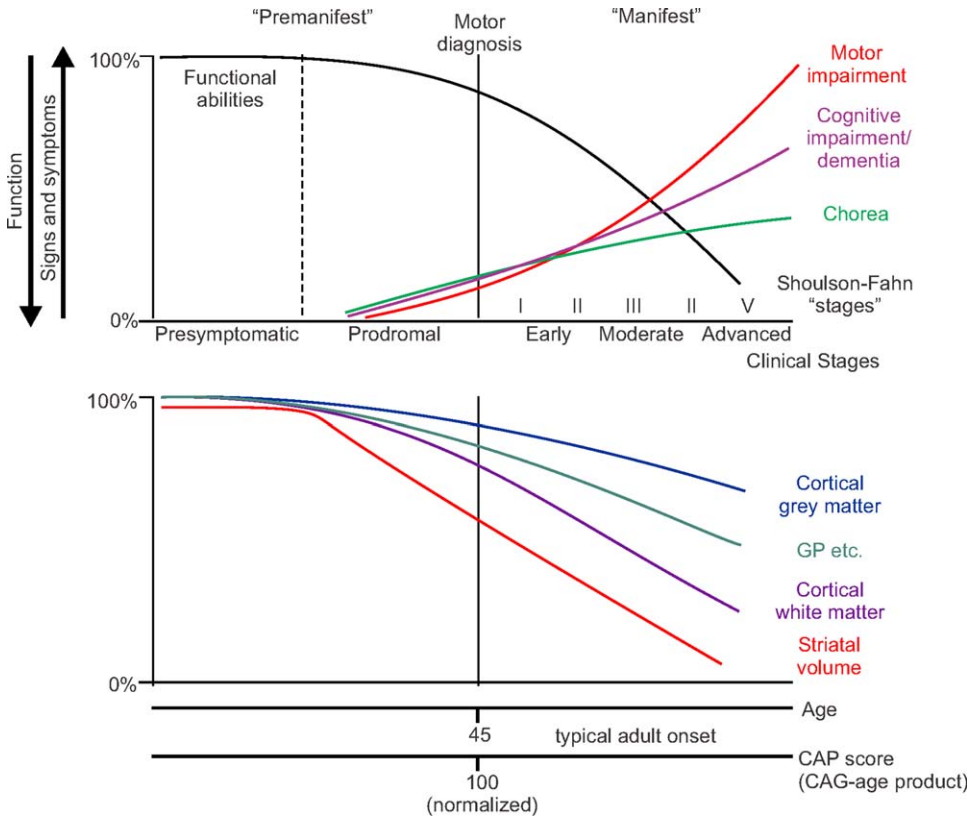

FIG. 1. Natural history of clinical HD, and hypothesized changes in imaging biomarkers. The normalized CAP score enables progression of many individuals with different CAG expansion lengths to be plotted on the same graph. Mean disease onset is at CAP score of approximately 100 (typically approximately 45 years of age), but substantial inter-individual variability exists. Without "normalization," the CAP score at onset exceeds 400. (**A**) Natural history. The period before diagnosable signs and symptoms of HD appear is termed "premanifest." During the "presymptomatic" period, no signs or symptoms are present. In "prodromal" HD, subtle signs and symptoms are present. Manifest HD is characterized by slow progression of motor and cognitive difficulties, with chorea often prominent early but plateauing or even decreasing later. Fine motor impairments (incoordination, bradykinesia, and rigidity) progress more steadily. (**B**) Hypothetical trajectory of several imaging biomarkers (best estimate based on current data: the PREDICT-HD and TRACK-HD studies have not followed individuals across the entire range of HD). The globus pallidus is a representative subcortical structure. Although overall cortical gray matter atrophy occurs at a late stage, more pronounced cortical layer–specific degeneration may occur earlier. Abbreviations: CAP, CAG age product; HD, Huntington disease. Modified from Ross et al.[20]

blood cells or cerebrospinal fluid may be changed,[22] but again no clinical impact is detectable. At this stage, by definition, no symptomatic treatment would be appropriate. However, in the future, disease-modifying treatments might begin, when safe and available.

Huntington's Disease—Genetically Confirmed—Prodromal (G10.1.2)

Prodromal HD may comprise a substantial period of time, possibly up to 10 years or more in some cases, before a clear and unequivocal diagnosis of manifest HD can be made. The brain changes beginning in the presymptomatic period eventually result in early motor signs, including subtle deficits in motor coordination and equivocal or slight choreiform movements.[6,23] Quantitative motor assessments likely show changes at this stage.[9,14] The motor DCL would be presumed to be 2, that is, changes that may be attributable to HD but not clinically confident. Slight cognitive deficits also commonly begin[19,24-26] In addition, there may be subtle changes in personality, including irritability and apathy, in prodromal HD.[6,9]

Major depression is common in individuals with the CAG expansion, but it can occur at any time during the natural history of HD,[27] including very far from motor onset. Major depression is quite common in individuals who do not have the CAG expansion causing HD,[28] and in HD it is not usually distinguishable from depression outside of HD.[29] In addition, depression is usually very treatable. For these reasons, we propose not to use major depression as a sole criterion for establishing the diagnosis of prodromal HD. However, major depression is a diagnosis of its own and would certainly be a focus of treatment. If major depression is accompanied by subtle motor problems and cognitive changes (not related to the depression itself), then depression could be part of the picture supporting a diagnosis of prodromal HD.

In prodromal HD, signs and symptoms would be presumed to have only minor impact on the function

TABLE 1. Huntington's Disease (G10)*

HD Genetically Confirmed (G10.1)		HD NOT Genetically Confirmed (G10.2)
Presymptomatic HD (G10.1.1) HD, genetically confirmed, presymptomatic	– No clinical motor signs or symptoms (Motor DCL = 0 or 1) – No cognitive signs or symptoms – May or may not have changes in imaging, quantitative motor assessments, or other biomarkers – No symptomatic treatment indicated – Disease-modifying treatment when safe and available	Clinically At-Risk for HD (G10.2.1) HD, not genetically confirmed, clinically at-risk
Prodromal HD (G10.1.2) HD, genetically confirmed, prodromal	– Subtle motor signs (usually Motor DCL = 2) – AND/OR subtle cognitive signs or symptoms – Minor decline from individual premorbid level of function may be detectable, but not required and not detectable on TFC – Apathy or depression or other behavioral changes judged related to HD may be present – Usually changes in imaging and quantitative motor assessments – May or may not require symptomatic treatment, eg, for depression – Disease-modifying treatment appropriate	Clinically Prodromal HD (G10.2.2) HD, not genetically confirmed, clinically prodromal
Manifest HD (G10.1.3) HD, genetically confirmed, manifest	– Presence of clinical motor and/or cognitive signs and symptoms that have an impact on life, with – Functional changes, eg, decrease in TFC – Motor DCL = 3 or 4 (or Motor DCL of 2 if cognitive changes are significant AND there is evidence of progression) – Symptomatic and disease-modifying treatment appropriate	Clinically Manifest HD (G10.2.3) HD, not genetically confirmed, clinically manifest (requires Motor Dx confidence = 4 plus cognitive changes)

*G10 is the classification for HD in the current "International Classification of Diseases" [ICD-10-GM-2014] published by the World Health Organization (WHO)—see http://apps.who.int/classifications/icd10/browse/2010/en#/G10. We here propose new subcategories for the G10 diagnosis.

of patients; in other words, some intra-individual decline may occur from the premorbid level of functioning, but it is not usually detectable on the Total Functional Capacity (TFC). Symptoms may or may not require symptomatic treatment, and disease-modifying treatment is appropriate when available.

Huntington's Disease—Genetically Confirmed—Manifest (G10.1.3)

We propose the final diagnostic category of "manifest" HD (and not the term "symptomatic" HD, because some subtle symptoms and signs begin during prodromal HD). "Manifest HD" is well-accepted as a term in HD research.[8,23] The diagnostic confidence level would usually be 3 or 4; in other words, the clinician is 90% (or greater) confident that motor changes are caused by HD. We do not believe it is appropriate to set a total motor score cutoff, because the significance of the motor score will vary greatly depending on whether evidence of change is seen or whether the baseline is high (eg, the patient has always been a bit clumsy or "twitchy"). However, we would point out, in the era of genetic testing, and especially when a patient has been followed longitudinally, and characteristic motor changes are clearly new, that the clinical diagnosis of HD may be achieved relatively early. For instance, a clinician may be quite confident that a subject, who previously had a TMS of 0, and now has developed slowing of saccades, slight dysdiadochokinesis, slight chorea, and difficulty with tandem gait, has manifest HD, even with a motor score of 5 to 10 points.

Cognitive changes are also likely to be present at this point, although for many subjects initial cognitive changes occur later than initial motor changes.[30] However, at this point, identifying a specific cognitive test that would deliver a cutoff for declaring a subject is manifest is difficult. Screening tests such as the Mini-Mental State Examination or Montreal Cognitive Assessment (MoCA) may demonstrate only minor changes. In a few cases, initial cognitive changes may precede initial motor changes, although in our experience, by the time a patient has cognitive change consistent with manifest HD, generally detectable motor findings are present. If cognitive symptoms (apart from those explainable by depression) are significant and evidence of progression is seen, a diagnosis of manifest HD should be considered

even if the motor DCL is 2. This indicates the importance of taking into account previous examinations, including previous UHDRS examinations, and all available history, as noted previously.

Manifest disease is expected to have an impact on function in everyday life and is predictive of future disease progression. Thus, clear changes should be present in the functional scales of the UHDRS, such as the TFC and Functional Assessment,[9,31,32] which can be clearly attributed to HD and not some other condition, for the diagnosis of manifest HD. Other assessments may become available in the future,[33,34] but will have to undergo further development and testing. Symptomatic and disease-modifying therapy are appropriate in this stage.

Huntington's Disease—Not Genetically Confirmed (G10.2)

We propose that those with "not genetically confirmed" HD also may be divided into three main categories, and these should also be specified in the International Classification of Diseases:

Huntington's Disease—Not Genetically Confirmed—At-Risk (G10.2.1)

These subjects have first-degree relatives with a diagnosis of HD or genetically tested for HD. They have not been genetically tested and do not exhibit any motor, behavioral (except possibly depression or other problems not clearly related to HD), or cognitive symptoms or functional decline (UHDRS-TFC and UHDRS-Functional Assessment normal). If they have a parent at risk, then they have a 25% risk.

Huntington's Disease—Not Genetically Confirmed—Clinically Prodromal (G10.2.2)

This diagnostic category has comparable clinical criteria to genetically confirmed prodromal HD, but the confirmation of genetic CAG extension is missing.

Huntington's Disease—Not Genetically Confirmed—Clinically Manifest (G10.2.3)

Similar criteria are applied as in the genetically confirmed cohort, but because phenocopy syndromes cannot be excluded, subjects without genetic proof of their CAG status should be diagnosed as clinically manifest when they have a diagnostic confidence of 4 rather than 3.

Implications

We believe the diagnostic categories proposed here are timely and are based on an improved knowledge of natural history and biomarkers of HD. We believe that this terminology will facilitate a better understanding of HD, similar to the previous change in terminology from "Huntington's chorea" to "Huntington's disease." They also reflect the trend in a number of disease areas of defining disease earlier based on biology and not just on the most severe clinical outcomes. Similarly, in osteoporosis, we do not wait until a fracture manifests to make a diagnosis and initiate treatment. Human immunodeficiency virus disease is defined now by biology and not just by late outcomes of immune compromise or cancer. Relevant to HD is the example of neurodegenerative diseases, such as Alzheimer's disease, in which mild cognitive impairment is increasingly seen as an important early stage. Huntington's disease is unique among the common neurodegenerative diseases in that all cases are caused by a single mutation for which genetic testing is available.

A number of issues should be considered in deciding how to evaluate changes in motor, cognitive, and emotional function. We have continued the use of the terminology of the DCL. We appreciate that this is imperfect and has a subjective quality. An alternative might be to use cutoffs for the motor score. However, the DCL of the UHDRS has the advantage of incorporating clinical judgment. Individuals may have findings on motor examination attributable to many causes besides HD, such as mild developmental disabilities, traumatic brain injury, and so forth, the pattern of which can be judged as "nonspecific" with regard to HD. Another issue is what kind of cognitive assessment to use. Unlike motor examination, in which the theoretical normal is a zero on the TMS, the cognitive ability of individuals is quite variable. No single cognitive test has general acceptance. Therefore, we have not specified any particular cognitive tests, but essentially leave that to clinical judgment. We also have incorporated consideration of emotional changes in the prodrome, but not as criteria for manifest HD. This is because emotional changes are common in the absence of HD, do not show a clear relationship to HD progression,[9,27] and in many cases (especially depression) are eminently treatable and reversible.

Diagnostic criteria focused on high specificity of diagnosis of manifest disease were desirable before the availability of genetic testing and before our expanded knowledge of the natural history of HD. Diagnoses based on the presence of subtle signs and symptoms were shown to result in false positives.[35] However, the availability of reliable genetic testing and the characterization of the early natural history now increases the sensitivity and specificity of HD diagnosis.

Use of these expanded diagnostic categories will require education of clinicians and patients and families. With growing knowledge, we have a duty to fully inform our patients and help them interpret this information adequately. Thus, HD expansion carriers will be in a better position to judge the possible risks and benefits of participation in clinical trials, particularly in the premanifest stage.

Stigmatization and discrimination are frequent in people at risk for HD,[36,37] and fear of being subject to either threat may be bigger than their actual incidences,[38] all issues that should be amenable to counseling, which may improve quality of life early on.

Early diagnosis will facilitate the development of novel therapies for HD. Several novel therapeutic options under development for HD may be more efficacious when tested in earlier stages of the disease process.[34,39] Our new diagnostic categories should facilitate the access of CAG expansion carriers to clinical trials, and thus the development and evaluation of such therapies. If effective disease-modifying therapeutics can be started during the presymptomatic or prodromal periods, HD may become an excellent example of the possibilities of personalized preventive medicine.

Earlier diagnosis also may facilitate the provision of programs for relatives and caregivers. If potential behavioral and cognitive problems are explained and caregivers receive appropriate support, including counseling and background information, this will likely benefit the patient and lead to improvement in their social surroundings.

A change of diagnostic criteria and categories is an important step for any field. We here present our view of a possible pragmatic solution. Nevertheless, we acknowledge that although we achieved agreement for the criteria and categories presented here, this was preceded by intense discussions, which highlights the need for exchange when defining the way forward in the field. We therefore suggest the initiation of a task force of the Movement Disorders Society, which will consult with all relevant stakeholders and develop a plan and proposal for revising the diagnostic criteria of HD, with the proposal introduced here being the starting point of a productive discussion. ■

References

1. Hogarth, P, Kayson, E, Kieburtz, K, et al. Interrater agreement in the assessment of motor manifestations of Huntington's disease. Mov Disord 2005;20:293-297.
2. Huntington Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord 1996;11:136-142.
3. Biglan, KM, Zhang, Y, Long, JD, et al. Refining the diagnosis of Huntington disease: the PREDICT-HD study. Front Aging Neurosci. 2013;5:12. doi: 10.3389/fnagi.2013.00012
4. 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;79:874-880.
5. 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. doi: 10.3389/fnagi.2014.00078.
6. Tabrizi SJ, Langbehn DR, Leavitt BR, et al. Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: cross-sectional analysis of baseline data. Lancet Neurol 2009;8:791-801.
7. Tabrizi SJ, Scahill RI, Durr A, et al. Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. Lancet Neurol 2011;10:31-42.
8. Tabrizi SJ, Reilmann R, Roos RA, et al. Potential endpoints for clinical trials in premanifest and early Huntington's disease in the TRACK-HD study: analysis of 24 month observational data. Lancet Neurol 2012;11:42-53.
9. 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;12:637-649.
10. Aylward EH, Harrington DL, Mills JA, et al. Regional atrophy associated with cognitive and motor function in prodromal huntington disease. J Huntingtons Dis 2013;2:477-489.
11. Aylward EH, Nopoulos PC, Ross CA, et al. Longitudinal change in regional brain volumes in prodromal Huntington disease. J Neurol Neurosurg Psychiatry 2011;82:405-410.
12. 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;71:822-828.
13. Aylward EH, Sparks BF, Field KM, et al. Onset and rate of striatal atrophy in preclinical Huntington disease. Neurology 2004;63:66-72.
14. Bechtel N, Scahill RI, Rosas HD, et al. Tapping linked to function and structure in premanifest and symptomatic Huntington disease. Neurology 2010;75:2150-2160.
15. Sturrock A, Laule C, Decolongon J, et al. Magnetic resonance spectroscopy biomarkers in premanifest and early Huntington disease. Neurology 2010;75:1702-1710.
16. Scahill RI, Hobbs NZ, Say MJ, et al. Clinical impairment in premanifest and early Huntington's disease is associated with regionally specific atrophy. Hum Brain Mapp 2011;10.
17. Delmaire C, Dumas EM, Sharman MA, et al. The structural correlates of functional deficits in early huntington's disease. Hum Brain Mapp 2012;10.
18. Paulsen JS. Cognitive impairment in Huntington disease: diagnosis and treatment. Curr Neurol Neurosci Rep 2011;11:474-483.
19. Stout JC, Jones R, Labuschagne I, et al. Evaluation of longitudinal 12 and 24 month cognitive outcomes in premanifest and early Huntington's disease. J Neurol Neurosurg Psychiatry 2012;83:687-694.
20. Ross CA, Aylward EH, Wild EJ, et al. Huntington disease: natural history, biomarkers and prospects for therapeutics. Nat Rev Neurol 2014;10:204-216.
21. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. [see comments]. Cell 1993;72:971-983.
22. Massai L, Petricca L, Magnoni L, et al. Development of an ELISA assay for the quantification of soluble huntingtin in human blood cells. BMC Biochem 2013;14:34. doi: 10.1186/1471-2091-14-34
23. Biglan KM, Ross CA, Langbehn, DR, et al. Motor abnormalities in premanifest persons with Huntington's disease: the PREDICT-HD study. Mov Disord 2009;24:1763-1772.
24. Stout JC, Paulsen JS, Queller S, et al. Neurocognitive signs in prodromal Huntington disease. Neuropsychology 2011;25:1-14.
25. Harrington DL, Smith MM, Zhang Y, et al. Cognitive domains that predict time to diagnosis in prodromal Huntington disease. J Neurol Neurosurg Psychiatry 2012;83:612-619.
26. Paulsen JS, Long JD. Onset of Huntington's disease: Can it be purely cognitive? Mov Disord 2014;29:1342-1350.
27. Duff K, Paulsen JS, Beglinger LJ, et al. Psychiatric symptoms in Huntington's disease before diagnosis: the predict-HD study. Biol Psychiatry 2007;62:1341-1346.
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;47:1423-1431.
29. Scaria J, Craufurd D. Clinical features of depression in huntington's disease: a cross sectional study comparing the clinical features of depression in patients with huntington's disease and in patients without huntington's disease. J Neurol Neurosurg Psychiatry 2014;85:e3-308883.

30. Ross CA, Pantelyat A, Kogan J, et al. Determinants of functional disability in Huntington's disease: Role of cognitive and motor dysfunction. Mov Disord 2014;29:1351-1358.

31. Marder K, Zhao H, Myers RH, et al. Rate of functional decline in Huntington's disease. Huntington Study Group [published erratum appears in Neurology 2000;54:1712]. Neurology 2000;54:452-458.

32. Beglinger LJ, O'Rourke JJ, Wang C, et al. Earliest functional declines in Huntington disease. Psychiatry Res 2010;178:414-418.

33. Brossman B, Williams JK, Downing N, et al. Development of the Huntington disease work function scale. J Occup Environ Med 2012;54:1300-1308.

34. Sampaio C, Borowsky B, Reilmann R. Clinical trials in Huntington's disease: Interventions in early clinical development and newer methodological approaches. Mov Disord 2014;29:1419-1428.

35. de Boo G, Tibben A, Hermans J, et al. Subtle involuntary movements are not reliable indicators of incipient Huntington's disease. Mov Disord 1998;13:96-99.

36. Bombard Y, Veenstra G, Friedman JM, et al. Perceptions of genetic discrimination among people at risk for Huntington's disease: a cross sectional survey. BMJ 2009;338:b2175. doi: 10.1136/bmj.b2175

37. Bombard Y, Palin J, Friedman JM, et al. Beyond the patient: the broader impact of genetic discrimination among individuals at risk of Huntington disease. Am J Med Genet B Neuropsychiatr Genet 2012;159B:217-226.

38. Erwin C, Williams JK, Juhl AR, et al. Perception, experience, and response to genetic discrimination in Huntington disease: the international RESPOND-HD study. Am J Med Genet B Neuropsychiatr Genet 2010;153B:1081-1093.

39. Wild EJ, Tabrizi SJ. Targets for future clinical trials in Huntington's disease: What's in the pipeline. Mov Disord 2014;29:1434-1445.