

Huntington Study Group's Neuropsychology Working Group: Implementing Non-Motor Diagnostic Criteria

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Abstract: Background: The clinical diagnosis of manifest Huntington's disease (HD) relies on a high level of clinical confidence (99% confidence) of HD-consistent motor signs. Longitudinal data have reliably identified cognitive and behavioral dysfunction predating clinical motor diagnosis by up to 15 years. Reliance on motor signs to establish a diagnosis of HD increases risk of early misdiagnosis or delayed diagnosis. Clinical neuropsychologists are uniquely positioned to advise on the clinical application of the Movement Disorder Society Task Force's recently proposed non-motor diagnostic criteria for HD.

Objectives: To provide (1) a recommended clinical approach toward non-motor diagnostic criteria in persons with HD and facilitation of accurate diagnosis; (2) recommended practices for medical treatment providers to screen and longitudinally monitor non-motor signs of HD.

Methods: The Huntington Study Group re-established the Neuropsychology Working Group, then recruited a multi-disciplinary group of neuropsychologists, neurologists, and psychiatrists to conduct an unstructured literature review and discuss expert opinions on practice, to facilitate an informal consensus opinion to accomplish the objectives.

Results: The opinion and an example protocol for medical treatment providers to screen, monitor, and triage non-motor signs and symptoms of Huntington's disease is provided.

Conclusions: Clinical diagnosis of non-motor HD is empirically justified and clinically important. Screening and triage by non-neuropsychologist clinicians can aid in detecting and monitoring non-motor Huntington's disease manifestation. The Neuropsychology Working Group consensus advances good clinical practice, clinical research, and quality of life. A companion position paper presenting the details of our consensus opinion regarding evidence-based guidelines for neuropsychological practice is forthcoming.

Huntington's disease (HD) is an inherited neurodegenerative condition characterized by progressive movement, cognitive, and psychiatric dysfunction. Standard clinical practice for diagnosis of manifest HD relies on motor criteria, whereby a clinician has 99% confidence that extrapyramidal movement signs are consistent with HD criteria in a person with a family history of HD or

genetic testing indicating that the person is an HD gene expansion carrier. However, longitudinal data indicate that predominantly cognitive and behavioral/psychiatric phenotypes are common, even a plurality, in persons with HD.^{1,2} Non-motor signs of sufficient severity to cause functional impairment often emerge a decade or more before clinical motor decline.³ These

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cognitive and behavioral changes, while often overlooked, can profoundly impact a person with HD's life, affecting their ability to work, maintain relationships, and participate in family life.⁴ While these changes encompass a broad spectrum in terms of severity and manifestations, they can, in a minority of cases, also result in unlawful behaviors.^{5,6} The burden of these non-motor symptoms often surpasses that of the motor symptoms, underscoring the necessity of their recognition and management.

People who exhibit cognitive and neuropsychiatric signs and symptoms may be diagnosed with symptomatic/syndrome-based disorders rather than HD (eg, early psychiatric symptoms may be diagnosed as bipolar disorder), frequently in cases of non-motor symptom predominant prodromes and/or when specialist care is difficult to access.⁷ These instances delay or mislead clinical intervention, prognosis, and functional planning. Eligibility for clinical trials and studies is also affected by exclusive reliance on motor signs for a diagnosis of HD; persons with predominantly non-motor manifestations of HD pathology are often missed in recruitment efforts for large-scale longitudinal studies, perpetuating a cycle of defining and confirming motor signs as the only valid method of disease diagnosis for HD.⁸ While large-scale registries have measured and documented subtle cognitive impairment and associated functional decline years prior to clinical motor diagnosis (eg, TRACK-HD,⁹ PREDICT-HD,¹⁰ PHAROS¹¹), the patient populations for most therapeutic trials have usually been stage I/II (early clinical diagnosis) per motor and functional scores of the Unified Huntington's Disease Rating Scale (UHDRS),¹² based in part on the motor outcome measures being amenable to detecting treatment-effect. A by-product of the motor-contingent diagnostic criteria and use as clinical-trial end-point is a relatively lesser attention for development and analysis of novel disease-modifying therapies for HD pathology in persons manifesting predominantly non-motor symptoms. The HD-ISS staging system is a recently developed research diagnostic criteria that includes a cognitive impairment component, though the factor is assessed via a single measure and the ISS is not designed or intended for clinical application.¹³

The authors determined that pursuing a "white paper" type report to the field would help address these issues; specifically, providing (1) a recommended clinical approach toward non-motor diagnostic criteria in persons with HD and facilitation of accurate diagnosis; (2) recommended practices for medical treatment providers to screen and longitudinally monitor non-motor signs of HD.

Methods

To begin to address these issues, the movement disorder society (MDS) commissioned a Task Force on HD Diagnostic Categories, to discuss and produce a set of recommendations for classification of HD that considers cognitive signs. Briefly, the Task Force highlighted the importance of cognition and recommended the use of the Diagnostic and Statistical Manual, Fifth Edition (DSM-5)¹⁴ for diagnostic purposes. However, consensus was reached to retain motor criteria for diagnosis of

HD. The aim of this paper is to further the conversation regarding the inclusion of cognitive signs in the diagnosis of HD.

Neuropsychologists specialize in assessing brain-behavior relationships in the clinical setting via integration of clinical history with empirically validated examination of cognitive performance and behavioral/emotional symptoms. Neuropsychological evaluation informs differential diagnoses, improves sensitivity in monitoring of clinical status, and guides the multidisciplinary treatment plan for persons with neurobehavioral disorders. Thus, neuropsychologists with expertise in HD are well-positioned to offer opinions on how to approach non-motor diagnostic criteria in HD and protocols for medical treatment providers to screen and longitudinally monitor non-motor signs of HD.

The Huntington Study Group (HSG) re-established its dormant Neuropsychology Working Group (NPWG) in 2019 (Co-Chairs: CMC, MAR). The NPWG recruited a group of neuropsychologists (CMC, MAR, VDB, KA, SAA, ASC, ALN-S, AP, JCS) with a combination of clinical, research, and HD-specific leadership exceeding 10 decades in combination. To ensure multi-disciplinary input, the group recruited two physicians with a combined five decades of experience in clinical and research related to neurological and psychiatric aspects of HD, along with well-defined HD-specific leadership roles (ALT, MCE). The group met monthly and engaged in continual email communications to discuss these objectives over a 6 month period in 2021–2022. This position paper summarizes the consensus opinion of the group regarding (1) recommended clinical approach toward non-motor diagnostic criteria in persons with HD and facilitation of accurate diagnosis; (2) recommended practices for medical treatment providers to screen and longitudinally monitor non-motor signs of HD. The HSG Research Advisory Council (RAC) reviewed this opinion and comments were considered and integrated. This content is intended for consideration across all levels and domains of clinical providers who work with HD populations. A companion position paper by the same group outlines the consensus opinion of the NPWG regarding best clinical neuropsychological practice guidelines for working with persons with HD.

Results

Objective 1: Non-Motor Clinical Diagnostic Criteria in HD

Historical Perspective

Initial investigations regarding cognitive deficits preceding motor manifestation of HD began more than 40 years ago. Prior to the availability of genetic testing, studies from the 1970s and early 1980s showed that subtle cognitive deficits could be detected several years before clinical motor diagnosis of HD, suggesting that cognitive changes could be a potential predictor of HD.¹⁵ In the late 1980s and early 1990s, studies with persons who were at high risk of developing HD as determined via linkage analysis showed mixed findings, with some noting the presence of

cognitive impairments in executive functions, visuospatial functions, and memory,¹⁶ and some not detecting group differences in cognition between high- and low-risk individuals.¹⁷ After analysis to identify mutation carriers became available in 1993,¹⁸ several more studies of cognitive impairment in pre-diagnosis individuals were published. Thereafter, attempts to address methodological limitations in the previous investigations produced an equivocal landscape, with some data demonstrating significant cognitive impairment in at-risk individuals^{19,20} and some failing to detect a difference compared to non-HD CAG expansion carriers.^{15,21,22}

In the last decade, there has been increased advocacy for integrating non-motor signs into the HD diagnostic schema.²³ Paulsen argued that cognitive signs should carry more weight in diagnostic criteria given their significant impact on functional decline and family burden, as well as the protracted period of cognitive deficit that can precede motor manifestation of HD.²⁴ A large-scale, international study of prodromal cognitive impairment, Predict-HD, solidified the robustness of cognitive impairment as a clinical indicator of manifest HD.²⁵ Duff and colleagues showed that nearly 40% of pre-diagnosed HD CAG expansion carriers in the Predict-HD study met formal criteria for Mild Cognitive Impairment when using comparative normative data from at-risk gene-negative participants.²⁶ However, a specific diagnostic approach incorporating non-motor signs of HD was not introduced until recently by Ross and colleagues²⁷ following the first explicit discussion of using cognitive exam findings in the diagnostic context.²⁸

Movement Disorder Task Force Diagnostic Approach: Neurocognitive Disorder Due to Huntington's Disease

The NPWG reached a consensus supporting the approach outlined by the MDS Task Force.²⁷ The MDS Task Force reviewed

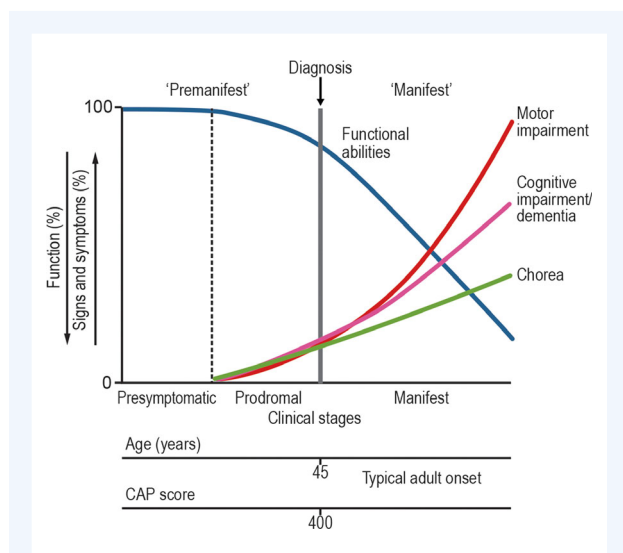


Figure 1. Clinical stages of Huntington's disease. Image is used under open-source agreement of the associated publication, with acknowledgement to Ross and colleagues.¹⁸

clinical and research definitions of HD in 2017 to offer updated nosology incorporating non-motor signs into the diagnostic process. First, the Task Force proposed a new lexicon separating HD into Premanifest and Manifest stages. The Premanifest stage was further subdivided into a pre-symptomatic stage, for those with confirmed HD CAG expansion who exhibited no motor signs; and a prodromal stage, for those who exhibited detectable motor signs that were not yet sufficient to warrant a diagnosis of HD (see Fig. 1). With regard to integrating non-motor signs into the manifest diagnosis, the Task Force noted that (1) longitudinal studies have thus far not supported the presence of significant cognitive impairment without at least the presence of detectable motor signs, and (2) the most common psychiatric symptoms of HD (eg, apathy, irritability, depressive suicidality, anxiety) are non-specific to HD CAG expansion carriers. Thus, the group advised combining the Diagnostic Confidence Level (DCL) template used for motor-based diagnosis of HD (see Table 1) with the DSM-5 approach toward diagnostic characterization of Mild and Major Neurocognitive Disorder (NCD; see Table S1). The specific Mild and Major NCD due to Huntington's Disease diagnostic criteria in the DSM-5 specifies that beyond the general criteria, there should be evidence of insidious onset and gradual progression, clinical (motor) manifest HD or risk due to family history or genetic testing, and the absence of a better explainable medical or mental condition. Whereas a motor-manifest diagnosis requires a DCL of 4, the task force proposed that a DCL of 3 combined with a Mild or Major NCD would represent manifest HD, and a DCL of 2 combined with either a Mild or Major NCD would represent prodromal HD (see Table 2).

Behavioral/Psychiatric Manifestations and their Impact on Cognition

Behavioral disorders and psychiatric phenomena are among the earliest and most functionally impairing signs of HD^{29–31} and can include anxiety, apathy, depression, irritability, perseveration, obsessions, and psychosis. However, the heterogeneity with which these symptoms are expressed in HD complicates their use as diagnostic criteria. For example, these symptoms tend to fluctuate non-linearly, and are subject to environmental and treatment factors.^{32,33} It is also debatable whether psychiatric and behavioral syndromes in HD can be separated into pathology-related syndromes (eg, apathy, irritability) and non-specific syndromes associated with HD (eg, PTSD, depressive

TABLE 1 HD diagnostic confidence levels

1. Symptoms mild, < 50% confidence
2. Symptoms possibly related to HD (50–89% confidence)
3. Symptoms probably related to HD (90–98% confidence)
4. Definitive HD motor signs (>99% confidence); Severity per Total Motor Score^{5–25}

Abbreviation: HD, Huntington's disease.

TABLE 2 Criteria for diagnosis in individuals with CAG-repeat expansion in Huntington’s disease

Diagnosis	Motor	Cognitive	Potential treatment
1. Presymptomatic HD	Dx conf 0–2	Normal	Disease modifying
2. Prodromal HD (either A or B)	A) Dx conf 2 B) Dx conf 3	A) + Minor or Major cognitive changes B) With normal/unchanged cognition	Symptomatic or disease modifying
3. Manifest HD (either A or B)	A) Dx conf 3 B) Dx conf 4	A) +Minor or Major cognitive changes B) With normal/unchanged cognition	Symptomatic or disease modifying

Note: Adapted from Ross et al.²⁷ Potential treatments apply to each of the 3 diagnoses regardless of the criteria for meeting the diagnosis. It is expected that the ability to define signs and symptoms would be enhanced by longitudinal follow-up and assessments. Recommend that neuropsychological testing be used to make determination of cognitive impairment; if necessary, an alternative quantified clinical assessment may be used to either document substantial impairment or document decline over time. Abbreviations: Dx conf, diagnostic confidence; HD, Huntington’s disease.

syndromes).^{34–36} That said, recent updates to diagnostic criteria, reflected in the DSM-5-TR, do provide specific codes for the presence/absence of “behavioral disturbance” even in the Mild NCD diagnosis; this represents a potential pathway of integrating neuropsychiatric symptoms into the overall formulation of non-motor symptoms into manifest HD diagnosis.

For these reasons, the NPWG reached the following consensus on the operationalization of MDS Task Force positions on behavioral/psychiatric manifestations in relation to cognitive signs in HD:

1. Although HD diagnostic criteria and staging systems (ie, the ISS, most recently) have traditionally excluded behavioral and psychiatric manifestations from their framework,²⁷ the presence of these symptoms in a confirmed HD CAG expansion carrier warrants close monitoring of cognitive and motor status.
2. The NPWG acknowledges that behavioral disorders are intrinsically and reciprocally linked to cognitive function.³⁷ For example, behavioral disorders (eg, anxiety, apathy) negatively affect cognitive functioning and influence the results of cognitive assessments. Further, common cognitive deficits in HD, such as early declines in social cognition, also have important implications for behavioral functioning.
3. The MDS Task Force did not address the DSM-5 approach toward capturing the presence of neuropsychiatric signs presumed related to the neuropathology producing the Neurocognitive Disorders (NCD), that is, “with or without behavioral disturbance.” The NPWG recommends using the “behavioral disturbance” modifier to incorporate documentation of behavioral/psychiatric manifestations of HD into a unitary NCD diagnosis, when the behavioral/psychiatric feature is favored to represent a neuropsychiatric syndrome associated with the HD pathology implicated in the NCD diagnosis itself. When this etiological connection is unclear, a separate primary psychiatric disorder diagnosis should be independently assigned.
4. The NPWG expects future research to delineate the presentation and course of neuropsychiatric signs in HD, including their association with other symptomatic dimensions and functioning, possibly leading to recognition of a predominantly behavioral HD phenotype.

Special Considerations in Clinical Application

The DSM-5 criteria for supportive evidence warranting a NCD is not absolute; the guidelines require evidence of significant or modest cognitive decline supported by patient/informant concern and impairment in cognitive performance. We strongly recommend that neuropsychological testing be used to make this determination, or if necessary, an alternative quantified clinical assessment should document decline over time. Depending on clinical setting, the upcoming ICD-11 terminology of Mild Neurocognitive Disorder and Dementia and associated criteria could easily be used with our recommendations. As applied to the HD population, there may be circumstances in which the patient is not concerned due to anosognosia; thus, an emphasis on the report of informant/collateral is important. Additionally, given the implications of assigning a manifest HD diagnosis, the field may wish to consider whether (a) recommendations for stricter severity of performance deficits (eg, >2 SD below normative expectations, rather than 1 or 1.5 SD) and (b) evidence of decline between two assessment points should be applied in this patient population to meet the gradual progression criteria (rather than report sufficing). Relatedly, discussion is warranted on if/how to operationalize the clinical confidence in the absence of better explaining medical or mental conditions criterion.

Finally, future discussion and empirical research is required to assess whether requiring a minimum DCL of 3 with NCD is useful or too stringent for a non-motor HD manifest diagnosis. In fact, it is the opinion of the authors that future consideration should be given to shifting the overall approach to diagnosis of HD to include: (1) a genetic diagnosis step, following confirmation of CAG expansion, and (2) assigning a symptomatic HD diagnosis in those genetic diagnosis HD patients who are judged to be presenting neurobehavioral symptomatology (ie, motor and/or non-motor features), which when taken as a whole and in the context of any clinically indicated additional diagnostics, is deemed probably attributable to HD pathology. Such a shift in diagnostic criteria would intentionally allow a diagnosis of symptomatic HD, in a confirmed genetic carrier, even in the absence of motor signs. Finally, the referring provider and clinical neuro-psychologist should both obtain informed consent from a motor

non-manifest, at-risk carrier, that undergoing neuropsychological evaluation may result in diagnostic evidence of manifest HD.

Objective 2: Protocols for Medical Treatment Providers to Screen and Longitudinally Monitor Non-Motor Symptoms of HD

With the goal of detecting possible non-motor manifestations of HD as early as possible, it is important that medical providers screen and monitor those at high risk of HD and those with concerning subclinical features of non-motor manifest HD. Following a positive screening, we recommend triage to appropriate specialists (eg, behavioral neurologist, neuropsychiatrist, movement disorders specialist, neuropsychologist, occupational therapist, genetic counselor) to aid in evaluating for a non-motor manifest HD diagnosis and to prevent false positive diagnosis. As previously mentioned, informed consent about the potential impacts of this non-motor workup should be obtained, given the implications of a possible manifest HD diagnosis being assigned.

Recommended Screening, Triage, and Monitoring of Cognitive, Psychiatric, and Functional Changes

Cognitive Screening Tests. We acknowledge that neuropsychological evaluation is not always feasible. In such circumstances, we recommend documentation of cognitive signs and symptoms, including by patients and caregivers when possible, and cognitive screening³⁸ with the caveat that cognitive screening *is not diagnostic or equivalent* to neuropsychological evaluation.^{39,40} Collateral informant reporting is important given the frequency of both denial and anosognosia in people with HD. Anosognosia can fluctuate based on disease stage and predisposing psychological factors.^{41–43} Additionally, language and cultural diversity factors should be considered to avoid false positives or negatives, both of which are possible.

If cognitive screening measures are the only means available, we recommend using a screening tool that has empirically demonstrated sensitivity and specificity to clinically significant cognitive impairment [ie, set at or near prodromal or mild cognitive impairment (MCI) cut-offs]. Similarly, the tool must have sensitivity across a range of cognitive severity such that it can detect cognitive signs across the range from pre-symptomatic to early-manifest disease stage. Furthermore, the measure should ideally have been characterized with respect to determining its Reliable Change Index,⁴⁴ so that if repeated screening is conducted, the clinician has the statistical basis to judge if there has been a significant change (ie, decline) in performance. The screening tool needs to assess multiple cognitive domains relevant to HD (attention/executive, memory, visuospatial, language) rather than focusing on a single aspect of cognition, such as memory. Moreover, the cognitive screening test should have demographically

adjusted norms and be developed from a study with a robust sample size that can provide the basis for judging the patient's performance. Formally translated screeners and suitable normative data are crucial when evaluating patients from various linguistic and cultural backgrounds to avoid pathologizing exposure-based factors (eg, education, occupation, culture) and incorrectly conceptualizing the individual as exhibiting cognitive impairment when none exists.^{45–47}

In 2017, MDS commissioned a subcommittee tasked with completing a systematic review of the professional literature to identify cognitive screening measures to evaluate “their context of use and validation in HD.”⁴⁸ Following an in-depth review of cognitive screening measures, no measures were designated as “recommended.” In their review, MDS designated the Montreal Cognitive Assessment (MoCA) as “recommended with caveats” for assessing the severity of cognition in HD and “suggested” for its ability to detect cognitive impairment.⁴⁸ While noting that the MoCA assesses a broad range of cognitive domains, the authors also identified that the utility of the MoCA is limited because it includes too few items to enable assessment of individual domains of cognition. Eight other cognitive screening measures met the “suggested” designation, a notch below the recommended category, including the Mini Mental Status Exam (MMSE), which is the most commonly used screening test for providing an overall measure of cognitive impairment in clinical and research settings.^{49,50} Primary critiques of the MMSE included limitations in assessing executive functions and insensitivity to assessing cognitive change over time. The Unified Huntington's Disease Rating Scale (UHDRS)-Cognitive Assessment also received “suggested” status, but it was judged to be constrained by its limited breadth with regard to cognitive constructs affected in HD and the lack of validation of the sum score.

In consideration of the MDS Task Force 2017 review, the NPWG recommends the MoCA for cognitive screening purposes when clinically indicated. Alternative screening measures can be found in Table 3. The MoCA meets many of the requirements previously outlined, including being more sensitive to cognitive dysfunction in HD when compared to the MMSE.^{38,51} Additionally, the MoCA's total score is corrected for education,⁵² providing some level of sensitivity for the potential confounding effects of limited demographic variables. However, we urge caution against over-reliance on, or over-exposure to, a single test such as the MoCA, particularly in the setting of clinical trials involving HD patients. Multiple versions of the MoCA are available and their use can help mitigate practice effects that may occur due to frequent exposure to the same test. Furthermore, we advocate for diversifying cognitive assessments, integrating other validated tests such as the UHDRS-Cognitive Assessment when appropriate. Though studies examining the MoCA's efficacy in longitudinally tracking cognition in HD populations are lacking, one study demonstrated the UHDRS-Cognitive Assessment's superior validity in monitoring cognitive changes in HD patients after 12 months, compared to the MoCA and MMSE.⁴⁴ As such, it may serve as a viable alternative in this context. Otherwise, we

TABLE 3 Example of screening measures for non-motor HD signs

Domain	Measure	Clinical criteria	Alternatives
Cognition	MoCA	Total score ≤26	MMSE, Kokmen, UHDRS-Cog SLUMS
Functional Status	WHODAS 2.0 (36 item)	None: 0–0.49 Mild: 0.5–1.49 Moderate: 1.5–2.49 Severe: 2.5–3.49 Extreme: 3.5–5	UHDRS-FAS/TFC/IS, Lawton-Brody iADL, FAQ
Mood	PHQ-9 GAD-7	Total score ≥5	HADS
Sleep-wake	ISI	Total score ≥8	PROMIS-SD-short & SRI-short, ESS, PSQI
Apathy	b-DAS	Executive subscale ≥4 Emotional subscale ≥5 Initiation subscale ≥6	AES
Dangerous Behaviors	C-SSRS-Screen BVC-short (last month)	C-SSRS-s Ideation ≥3 C-SSRS-s Behavior = 2 BVC-s ≥3	PHQ-9 item #9
Collateral Observations	NPI-Q	Clinical judgment per item	Clinical interview

Abbreviations: MoCA, Montreal Cognitive Assessment⁵²; MMSE-2, MiniMental Status Exam, Second Edition⁵⁴; Kokmen STMS, Kokmen Short Test of Mental Status⁵⁵; SLUMS, Saint Louis University Mental Status Examination⁵⁶; UHDRS-Cog, Unified Huntington’s Disease Rating Scale-Cognitive Function⁵⁷; UHDRS-TFC, Unified Huntington’s Disease Rating Scale-Total Function Capacity⁵⁷; WHODAS 2.0, World Health Organization Disability Assessment Schedule 2.0⁵⁸; Lawton-Brody iADL, Instrumental Activities of Daily Living⁵⁹; FAQ, Functional Activities Questionnaire⁶⁰; PHQ-9, Patient Health Questionnaire⁶¹; GAD-7, 7-item Generalized Anxiety Disorder Scale⁶²; HADS, The Hospital Anxiety and Depression Scale⁶³; ISI, Insomnia Severity Index⁶⁴; PROMIS, Patient-Reported Outcomes Measurement Information System; SD, Sleep Disturbance; SRI, Sleep-related Impairment⁶⁵; ESS, Epworth Sleepiness Scale⁶⁶; PSQI, Pittsburgh Sleep Quality Index⁶⁷; b-DAS, brief Dimensional Apathy Scale⁶⁸; AES, Apathy Evaluation Scale⁶⁹; C-SSRS-Screen, Columbia Suicide Severity Rating Scale Screen Version⁷⁰; BVC, The Broset Violence Checklist⁷¹; NPI-Q, Neuropsychiatric Inventory Questionnaire.⁷²

recommend the MoCA with the Chelune formula to assess for treatment response or progression of cognitive decline.⁵³ When an assessment is necessary for mid-stage HD patients, the UHDRS-FAP is a consideration but is limited by its need for further study in HD populations.⁴⁸ In addition to cognitive screening tests, the NPWG also recommends screening for behavioral and psychiatric signs and symptoms using well-established but brief symptom-reports (per patient and informant/s), discussed further below.

We recognize that the MoCA is globally acknowledged and frequently used among health professionals, and thus, we endorse its use for cognitive screening when clinically relevant. One aspect of this determination should be the frequency of, and interval between, administration of a cognitive screen. Practice-effects can impact diagnostic sensitivity and therefore delay detection of relevant symptomatology and/or impact clinical trial eligibility. The MoCA does have alternate forms, but it would be advisable to reserve use for annual visits or when clinical-functional status decline is reported. Furthermore, it is crucial to consider that other recommended screening tools may not be as universally

recognized or accessible, which could hinder their application in some circumstances. We advise considering this factor as a potential constraint when adapting our recommendations.

Functional Screening Measures. Functional status is important in determining the risk of early signs of non-motor manifestation of HD and important in forming recommendations. We suggest documenting functional status, ideally with comments (based on clinical judgment) as to whether the dysfunction is primarily related to non-motor or motor signs. We suggest screening for functional impairment, ideally using both a patient and a collateral informant questionnaire. The WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) is an open-source, self-report measure with an available proxy questionnaire that has a 36-item short-form (with 12-item brief version available), which covers basic activities of daily living (ADLs); instrumental ADLs; and high-complexity domains such as mobility, life activities, vocation, and interpersonal/social activity.⁷³ The inclusion of more complex functional domains increases sensitivity in patients with subtle symptoms impacting independence; additionally, both

versions have been psychometrically validated across HD stages.^{74,75} However, we should also acknowledge the more disease-specific and frequently used functional screens used in clinical-research with HD, namely the UHDRS sub-scales related with function: the 5-item clinician-patient/informant interview score for Total Functional Capacity, the expanded 25-item Functional Assessment Scale, and the single clinician-rated Independence Scale score. We suggest these as acceptable for substitution, though point out that each of psychometric weaknesses (namely, incomplete reliability testing) and low “ceilings” (reducing sensitivity in early stage/subtle symptom cases).⁷⁶ A new measure that bridges the advantages of the WHODAS and UHDRS functional sub-scales is the Functional Rating Scale 2.0, which may offer another option when available with validity data and cut-offs.⁷⁷ Please see Table 3 for additional recommendations and alternatives for functional assessment screening measures.

Behavioral/Psychiatric Screening Measures. Behavioral and psychiatric symptoms fluctuate, and therefore need to be considered frequently; these symptoms can impact the interpretation of cognitive and functional screening tools. We advise documenting the presence and severity of these symptoms per patient and collateral informant report.⁷⁸ Short-forms of questionnaires with empirically based cut-offs for clinically significant symptoms should be considered for depression, anxiety, apathy, and sleep-wake disturbance (Table 3). Screening for safety-related behavioral symptoms (ie, suicidality, aggression/violence toward others) should also be incorporated into the assessment due to the elevated incidence in HD and profound morbidity/mortality risk associated with the symptoms; a secondary benefit of including screening steps is ensuring the domain is not overlooked or forgotten during clinical contacts.^{79–82} Psychotic symptoms typically require clinical judgment based on comparing patient reports to observations and collateral reports, as well as monitoring for atypical behavioral manifestations in clinic. Finally, behavioral/psychiatric symptoms should also be noted independent from performance/report on screening measures. Both patient and collateral informant perspectives should be considered given the high incidence of anosognosia among HD patients.

Triage Response. For determining next steps, a triage approach is applied to the information gathered from a clinical interview in addition to the cognitive, functional, and behavioral/psychiatric screeners. This triage response will ensure that patients are referred to appropriate providers for follow-up, which will aid in supporting a non-motor manifest HD diagnosis if appropriate and facilitate treatment planning. An example is outlined in Table 4, which is intended to apply to new patients or those previously seen without elevated concern for clinically significant non-motor HD signs. In brief, we suggest that the screening results be organized into High, Moderate, Low, or Lowest risk of non-motor manifest HD. These categories are not substitutes for a neurocognitive or psychiatric diagnoses, nor do they represent a diagnostic impression on whether HD pathology is the

likeliest etiology for the symptoms. However, they do suggest reasonable next steps in the diagnostic workup.

Monitoring over Time. In the setting of the proposed triage model, we recommend follow-up monitoring for all HD patients. For those in the Lowest and Low categories, clinical judgment, established cut-scores, and RCI on the cognitive screen can be used to document the stability, or degree of progression, of the symptoms. Discussing the concept of baseline neuropsychological evaluation can have a role in the Lowest category and can be encouraged after appropriate management of modifiable comorbid confounds in the Low category. The triage categories and responses remain relevant in follow-up; however, the NPWG has identified several common referrals that warrant referral for full neuropsychological evaluation:

1. Is there evidence of marked cognitive and behavioral decline from baseline/prior assessment in a patient without an NCD or with Mild NCD due to HD?
2. Are cognitive and behavioral symptoms linked to functional decline or functional safety considerations (eg, access to firearms/weapons, heavy machinery, driving, independent management of medications, financial capacity, decision-making capacity)?
3. Is there a comorbid condition exacerbating HD dysfunction?
4. Is the patient applying for, or are they suited to disability, vocational rehabilitation services, or in-home care?

These are important clinical considerations regarding diagnosis (ie, transition to Major NCD) as well as available resources and treatment planning. Follow-up monitoring can also help track changes associated with treatment decisions, such as response or side-effects to HD-related medications and the management of comorbid conditions. Repeat assessments should be performed at the request of the patient or family. If an HD patient is high functioning and has a job that has significant financial and legal responsibilities (ie, judge, CEO, financial advisor), or safety concerns (eg, police, pilot, nurse, physician/surgeon), then baseline and repeat neuropsychological evaluations are essential. As we have described, a full neuropsychological evaluation is more sensitive than cognitive screeners for detecting cognitive impairment in high functioning individuals, such as physicians.^{83,84}

Some circumstances have a significant likelihood of not indicating follow-up for neuropsychological re-evaluation, and thus we advise consultation with the neuropsychologist prior to making a formal referral when possible. These circumstances include:

1. Neuropsychological decline consistent with the HD disease course in a patient already diagnosed with Major Neurocognitive disorder due to HD
2. Clinically unstable psychiatric presentation (active psychosis, hypo/mania, intoxication, substance abuse not yet in early remission)
3. Sensorimotor and/or non-verbal status precludes significant engagement in cognitive testing
4. Strong patient resistance or refusal (consider counseling)

TABLE 4 Example of screening categories & triage for patients at risk for non-motor HD signs

Category	Cognitive or psychiatric screens (consider patient & informant)	Motor symptoms	Functional Status (associated with non-motor symptoms)	Triage Response
Lowest risk	Asymptomatic, normal findings on cognitive and psychiatric screens	Asymptomatic	Intact	<ul style="list-style-type: none"> Screen acts as baseline, discuss pros/cons of proactive neuropsychological baseline evaluation Consider follow-up annually or as needed Offer psychosocial support and educational resources
Low risk	Subtle symptoms, normal findings on cognitive and psychiatric screens	Asymptomatic	Intact	<ul style="list-style-type: none"> Screen acts as baseline Discuss lifestyle and first-line treatment options for common reversible factors associated with cognitive or psychiatric symptoms Consider increasing frequency of visits / monitoring and discuss proactive neuropsychological baseline evaluation if no response
Modest risk	Atypical findings on cognitive and/or psychiatric screens	Asymptomatic or symptomatic	Intact	<ul style="list-style-type: none"> Consider first-line treatment option(s) for common reversible factors associated with cognitive/psychiatric symptoms Schedule near-term visits and refer to Neuropsychology if no improvement at follow-up.
High risk	Atypical findings on cognitive and/or psychiatric screens	Asymptomatic or symptomatic	Impaired	<ul style="list-style-type: none"> Initiate first-line treatment options & refer to Psychiatry/Neurology for a prescription consult or ongoing management Refer to Neuropsychology Consider referral to PT/OT/SLT Initiate safety procedures, near-term visits after stable to re-triage

Abbreviations: OT, occupational therapy; PT, physical therapy; SLT, speech-language therapy.

Of note, without a diagnostic confidence level characterization of motor symptoms, an HD-related NCD diagnosis is not possible using our proposed framework; thus, we would recommend a neurological exam prior to triage to neuropsychological evaluation, if possible. If such an examination is not immediately possible, a neuropsychologist may nonetheless diagnose a Major or Mild NCD, but the etiology would be unclear.

Conclusions

Clinical diagnosis of non-motor HD is empirically justified and clinically important. While a diagnostic approach differs from establishing research criteria, clinical practice and research are reciprocal and inextricably linked toward the pursuit of developing disease-modifying therapies for HD. Establishing a common lexicon and diagnostic approach for non-motor manifest HD signs and symptoms serves to increase our understanding of the implications of early detection and intervention on clinical outcomes across the spectrum of HD phenotypes. As the NPWG diagnostic approach has outlined in detail above, appropriate screening and triage by non-neuropsychologist clinicians can aid in detecting non-motor HD manifestation and effectively monitoring the complete clinical course of HD. Further expert discussion and empirical research is required to address the potential implications of applying this clinical approach, including (i) importance of collateral/informant concerns given anosognosia in the HD population, (ii) operationalization of impaired cognitive performance and insidious/progressive course, (iii) operationalization of clinical confidence that the supportive findings are HD related rather than alternative medical or mental condition, and (iv) informed consent clarifying the potential result of evaluation being a manifest HD diagnosis. Ultimately, accurately diagnosing these symptoms is not only good clinical practice, but also advances clinical research and lays the foundation for optimal quality of life for patients living with HD and their families. A companion position paper by the NPWG with a consensus opinion regarding evidence-based guidelines for neuropsychological practice is forthcoming.

Author Roles

(1) Research review project: A. Conception, B. Organization, C. Execution; (2) Qualitative Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

C.M.C.: 1ABC, 2ABC, 3AB

M.A.R.: 1BC, 2ABC, 3AB

V.A.D.B.: 1BC, 2ABC, 3AB

K.A.: 1BC, 2ABC, 3AB

S.A.A.: 1C, 2ABC, 3AB

A.S.C.: 1C, 2ABC, 3AB

M.C.E.: 1C, 2ABC, 3AB

A.L.N.S.: 1C, 2ABC, 3AB

A.P.: 1C, 2ABC, 3AB

A.T.: 1C, 2ABC, 3AB

J.C.S.: 1C, 2ABC, 3B

Ethical Compliance Statement

All procedures involved in this review were consistent with the regulations established by the Helsinki Declaration of the World Medical Association. Informed patient consent was not necessary for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. DSM-5, Diagnostic and statistical manual of mental disorders, fifth edition, text revision. HD, Huntington disease.