JOURNAL OF NEUROLOGY AND PSYCHOLOGY RESEARCH

CASE STUDY Open Access

Huntington's disease – IV. Clinical assessment, prevention and prognosis

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Received date: November 16, 2024, **Accepted date:** November 20, 2024, **Published date:** November 23, 2024.

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Abstract

There is currently no cure for Huntington's disease (HD) and no treatment proven to delay the onset or slow the progression of the disease. This Article discusses the several associated clinical assessment tests in their relevant particulars. The tests include the four major ones that are also employed in clinical trials, specifically, the Unified Huntington's disease rating scale; the Mini-mental status examination; the Beck's depression inventory scale; and the Columbia's suicide severity rating scale. Prevention of the disease and its prognosis are lastly addressed.

Abbreviations

AD: Alzheimer's disease; APA: American Psychiatric Association; BDI: Beck's Depression Inventory; CBT: Cognitive behavioral therapy; CoP: Computerized test; CSSRS: Columbia's Suicide Severity Rating Scale; DLB: Dementia with Lewy bodies; DSM: (APA's) Diagnostic & Statistical Manual of Mental Disorders; FCS: Functional capacity scale; GMSE: Geriatric mental state examination; GPAC: General practitioner assessment of cognition; HAMTS: Hodkinson's abbreviated mental test score; HD: Huntington's disease; HDRS: Hamilton Depression Rating Scale; HSG: Huntington Study Group; HTT: Huntington's gene; JHD: Juvenile HD; IS: Independence scale; KCDI: Kovac's Children Depression Inventory; MAPS: Mental attributes profiling system; MCI: Mild cognitive impairment; MMSE: Mini-mental status examination; MSE: Mental status examination; OQM: Objective quantitative motor; PD: Parkinson's disease; PDD: PD dementia; PHQ: Patient health questionnaire; SDMT: Symbol digit modalities test; SIT: Stroop interference test; TBS: Total behavioral score; TFCS: Total functional capacity score; TMS: Total motor score; UHDRS®: Unified Huntington's Disease Rating Scale; UHDRS - FAP:

UHDRS for advanced patients; VFT: Verbal fluency Test; vUHDRS: virtual UHDRS; VDD: Vascular disease dementia;

Keywords

Clinical trials; Huntington's disease; Huntington's gene; Clinical assessment tests; Unified Huntington's disease rating scale; Mini-mental status examination; Beck's depression inventory scale; Columbia's suicide severity rating scale; Prevention and prognosis.

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A variety of tests are employed in the clinical assessment of Huntington's disease (HD) patients and to quantify the results of clinical trials. They can also be used for the prevention of the disease and its prognosis. In this Article, I discuss these tests in all their particulars prior to embarking on the difficult tasks of prevention and prognosis of HD. I begin with the four major clinical assessment tests.

Unified Huntington's Disease Rating Scale

The Unified Huntington's Disease Rating Scale (UHDRS®) is a research tool which has been developed by the Huntington Study Group (HSG) to provide a uniform assessment of the clinical features and course of HD. It is the standard clinical assessment tool in HD. In patients with advanced HD, ceiling and floor effects of the scale hamper the detection of changes. Therefore, the UHDRS - For Advanced Patients (UHDRS - FAP) has been designed for patients with late - stage HD. The tool has undergone extensive reliability and validity testing and has been used as a major outcome measure by the HSG in controlled clinical trials.

Key component descriptors

The UHDRS was developed as a clinical rating scale to assess four domains of clinical performance and capacity in HD:

- **Motor function:** This domain includes 31 items with 5-point ordinal scale ranging from 0-4, the highest score indicating inability to perform the motor task.
- **Cognitive function:** This domain includes 3 items with higher scores indicating better cognitive performance: Verbal Fluency Test (VFT); Symbol Digit Modalities Test (SDMT); and Stroop Interference Test SIT). Higher scores indicate better cognitive performance.
- **Behavioral function:** This domain includes 10 items with a 5-point ordinal scale ranging from 0 to 4 with the highest score indicating severe behavioral symptoms; 4 items requiring the evaluator to answer (yes/no) questions (1 point for every 'yes' score) about the overall clinical impression with respect to the participant showing clinical evidence of confusion, dementia, depression, and requiring pharmacotherapy.
- **Functional capacity:** This domain is divided into three sections:

  - Total functional capacity scale (TFCS): It includes 5 items with 4-point ordinal scale ranging from 0 to 3, the highest score indicating higher functional capacity.
  - Functional capacity score (FCS): It is reported as the total functional capacity score (TFCS). It has a total of 25 (Yes/No) questions to assess the total functional capacity of the individual. A score of 1 is given to all 'yes' replies;

- Independence scale (IS): It is rated from 10 to 100 with higher scores indicating better functioning than lower scores.

Domain	Descriptor	Clinical performance
Motor function	o 31 items. o 5-point ordinal scale (0-4).	o Inability to perform the motor task. o Higher scores indicate inability to perform motor task.
Cognitive function	o 3 items: -Verbal Fluency Test (VFT). - Symbol Digit Modalities Test (SDMT). - Stroop Interference Test SIT).	o Higher scores indicate better cognitive performance.
Behavioral function	o 10 items (4 items require evaluator to answer 'yes/no' questions about overall clinical impression with clinical evidence of confusion, dementia, and depression requiring pharmacotherapy). o 5-point ordinal scale (0-4).	o Highest score indicates severe behavioral symptoms.
Functional capacity		
o Total functional capacity scale	o 25 'yes/no' questions assessing total functional capacity.	o Score of 1 given to all 'yes' replies.
o Functional capacity score	o 5 items 4-point ordinal scale (0-3).	o Highest score indicate higher functional capacity.
o Independence scale	o Rated from 10 to 100.	o Higher scores indicate better functioning.

Table 1: Domains of the Unified Huntington's Disease Rating Scale

Features of interest

The following features have been demonstrated: A high degree of internal consistency within each of the domains; significant intercorrelations between the domains, with the exception of the total behavioral score (TBS); and an excellent degree of inter-rater reliability for the motor scores.

The UHDRS may be useful for tracking changes in the clinical features of HD over time. It assesses relevant clinical features of HD and appears to be appropriate for repeated administration during clinical studies.

Updates

Two important updates and expansions of the UHDRS® have been made:

- **UHDRS®'99:** To augment the utility and applicability of this research tool, certain of its components were enhanced and guidelines were provided for use of the scale. In 2005 the Behavioral Assessment section was further clarified and refined based on research experience.

- **VUHDRS®:** The vUHDRS® (virtual Unified Huntington's Disease Rating Scale) is a way to use the UHDRS® remotely with consistency and excellent reliability. This version of the

tool breaks down accessibility barriers and allows for virtual assessments in HD trials as well as for virtual clinical assessment of patients with HD.

Total motor score

Deficits in motor function are a hallmark of HD. The Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) is a categoric clinical rating scale assessing multiple domains of motor disability in HD. It or subsets of its items have served as primary or secondary endpoints in numerous clinical trials. In spite of a well-established video-based annual online certification system, intra- and inter-rater variability, subjective error, and rater-induced placebo effects remain a concern. In addition, the UHDRS-TMS was designed to primarily assess motor symptoms in manifest HD.

Recently, advancement of technology resulted in the introduction of the Objective Quantitative-Motor (OQM) assessments in biomarker studies and clinical trials in HD. OQM measure detected motor signs in blinded cross-sectional and longitudinal analyses of manifest, prodromal, and premanifest HD cohorts up to two decades before clinical diagnosis. In a multicenter clinical trial in HD, Q-Motor measures were more sensitive than the UHDRS-TMS and exhibited no placebo effects. Thus, Q-Motor measures are currently explored in several multicenter trials targeting both symptomatic and disease-modifying mechanisms. They may supplement the UHDRS-TMS, increase the sensitivity and reliability in proof-of-concept studies, and open the door for phenotype assessments in clinical trials in prodromal and premanifest HD.

The Mini-Mental Status Examination

Background and Rationale

Cognitive function may decline as a result of certain risk factors (e.g., hypertension, elevated cholesterol, cardiac arrhythmias, HD symptoms, etc.). This, in turn, could adversely impact the physical functioning and quality of life of younger and older adults. Dementia is a major illness and cause of disability among the elderly, affecting also HD individuals.

The Mini-Mental Status Examination

The Mini-Mental Status Examination (MMSE), or Folstein test, is a widely used test of cognitive function. It includes tests of orientation, attention, memory, language, and visual-spatial skills. It consists of a 30-point questionnaire that is used extensively in clinical and research settings to:

- Measure cognitive impairment;
- Estimate the severity and progression of cognitive impairment;
- Follow the course of cognitive changes in an individual over time;
- Provide a diagnosis for any particular nosological entity (or classification of diseases); and
- Screen for dementia.

Administration of the test takes between 5 and 10 minutes and examines functions including:

- **Registration** (repeating named prompts);
- **Attention and calculation;**
- **Recall;**
- **Language;**
- **Ability to follow simple commands; and**
- **Orientation.**

It was originally introduced by Folstein *et al.* in 1975, in order to differentiate organic from functional psychiatric patient. It is very similar to, or even directly incorporates, tests which were previously in use. This test is not a mental status examination (MSE).

Advantages of the utilization of the MMSE

Advantages of the MMSE include:

- **Can be customized:** such as for use on patients who are deaf, blind, or partially immobilized;
- **Is useful for cognitive assessment in the clinician's office space or at the bedside:** due to its short administration period and ease of use;
- **Is valid and reliable for the diagnosis and longitudinal assessment of Alzheimer's disease** (AD);
- **Is increasingly reliable in comparisons:** it can differentiate between different types of dementias because of the consistent application of identical questions. For example: AD patients score significantly lower on orientation in time, place, and recall compared to vascular disease dementia (VDD) patients, patients with dementia with Lewy bodies (DLB), and Parkinson's disease dementia (PDD). However, systematic reviews of this test have shown no evidence to support this examination as a stand-alone, one-time test for identifying high-risk individuals who are likely to develop AD dementia (ADD)

Disadvantages of the utilization of the MMSE

Disadvantages of the utilization of the MMSE are that:

- It is affected by demographic factors (age and education exert the greatest effect);
- It lacks sensitivity to mild cognitive impairment (MCI);
- It fails to adequately discriminate patients with mild AD from normal patients;
- **No specialized equipment or training is required for administration;**
- It is insensitive to progressive changes occurring with severe AD; and
- It is uncertain at detecting focal lesions: because its content is highly verbal, lacking sufficient items to adequately measure visuospatial and/or constructional practice.

Other tests are also used, including the:

- **Hodkinson's Abbreviated Mental Test Score (HAMTS);**
- **Geriatric Mental State Examination (GMSE);**
- **General Practitioner Assessment of Cognition (GPAC);**
- **Computerized tests (such as CoPs);**
- **Mental Attributes Profiling System (MAPS); and**
- **Longer formal tests for deeper analysis of specific deficits.**

These other tests are not reviewed here as they would fall outside the scope of this article.

Features

The MMSE test includes simple questions and problems in a number of areas, including the:

- **Time and place of the test;**
- **Repeating lists of words;**
- **Arithmetic** (such as the serial sevens);
- **Language use and comprehension;** and
- **Basic motor skills** (such as copying a drawing of two pentagons).

Category	Possible points	Description
Orientation to	5	From broadest to most narrow. Orientation to time has been correlated with future

time		decline.
Orientation to place	5	From broadest to most narrow. This is sometimes narrowed down to streets and sometimes to floor.
Registration	3	Repeating named prompts,
Attention and calculation	5	Serial events (more appropriate for populations where English is not the first language); spelling 'world' backwards..
Recall	3	Registration recall.
Language	2	Naming a pencil and a watch.
Repetition	1	Speaking back a phrase.
Complex commands	6	Varies. Can involve drawing a figure..

Table 2: Point system of the MMSE

Score range	Cognitive impairment
24-30	Normal
19-23	Mild
10-18	Moderate
</= 9	Severe

Total number of points possible = 30

Table 3: Cognitive impairment based on the MMSE score

The official total score for the MMSE (i.e. the scores used for statistical analyses) are computer-generated. Examiners record individual test item scores on the MMSE test form. The one exception is "WORLD" where examiners record the response of subjects in the exact order that it is given by the subject.

Education-adjusted MMSE cut-off scores

The MMSE education-adjusted scores are indicated in Table 4. In general, participants scoring below education-adjusted cut-off scores on the MMSE may be cognitively impaired.

Score range	Education level	Cognitive impairment
26 or below	Some college or higher.	Normal.
25 or below	High school graduate.	Mild.
24 or below	8th grade or some high school.	Moderate.
22 or below	7th grade or below.	Severe.

*Note: The Education Adjusted Cut-off Scores are calculated by data management

Table 4: Education-adjusted MMSE cut-off scores

For referral purposes, any participant with a drop of 3 points in score since their last exam should be referred to a neurology group. A preliminary score can be calculated to determine if the participant should be referred. Any subject with MMSE at or above 26 may be presumed competent unless listed otherwise at the last evaluation. Some actors may potentially affect the MMSE testing, for example, when a participant is incapacitated by blindness, has a functional disability, is illiterate, or is otherwise unable to respond to a question. The single exception to scoring is if a participant is in a coma (this circumstance would be encountered in a nursing home visit).

Caveats

- **Correction for educational attainment and age:** The raw score achieved on the MMSE test may need to be corrected;
- **A maximum score of 30 points can never rule out dementia;**
- **Low to very low scores correlate closely with the presence of dementia:** although other mental disorders can also lead to abnormal findings;
- **Interference with the interpretation:** The presence of purely physical problems can interfere with the interpretation if not properly noted; for example, a patient may be physically unable to hear or read instructions properly or may have a motor deficit that affects writing and drawing skills.

Maximization of the benefits of the MMSE

In order to maximize the benefits of the MMSE the following recommendations from Tombaugh and McIntyre (1992) should be employed:

• "The MMSE should be used as a screening device for cognitive impairment or a diagnostic adjunct in which a low score indicates the need for further evaluation. It should not serve as the sole criterion for diagnosing dementia or to differentiate between various forms of dementia. However, the MMSE scores may be used to classify the severity of cognitive impairment or to document serial change in dementia patients;

• The following four cut-off levels should be employed to classify the severity of cognitive impairment: No cognitive impairment 24-30; mild cognitive impairment 19-23; moderate cognitive impairment 10-18; and severe cognitive impairment ≤9;

• "The MMSE should not be used clinically unless the person has at least a grade 8 education and is fluent in English. While this recommendation does not discount the possibility that future research may show that the number of years of education constitutes a risk factor for dementia, it does acknowledge the weight of evidence showing that low educational levels substantially increase the likelihood of misclassifying normal subjects as cognitively impaired;

• "Serial 7's and WORLD should not be considered equivalent items. Both items should be administered and the higher of the two should be used. In scoring serial 7's, each number must be independently compared to the prior number to ensure that a single mistake is not unduly penalized. WORLD should be spelled forward (and corrected) prior to spelling it backward;

• "The words apple, penny and table should be used for registration and recall. If necessary, the words may be administered up to three times in order to obtain perfect

registration, but the score is based on the first trial; and.

• "The 'county' and 'where are you' orientation to place questions should be modified: The name of the county where a person lives should be asked rather than the county of the testing site, and the name of the street where the individual lives should be asked rather than the name of the floor where the testing is taking place."

Beck's Depression Inventory or scale

Test development

The Beck's Depression Inventory (BDI) is one of the most widely used psychometric test for measuring the severity of depression. Its development was an important event in psychiatry and psychology in that it represented a shift in health care professionals' view of depression from a Freudian, psychodynamic perspective, to one guided by the patient's own thoughts or "cognition". Instead of attempting to develop a psychometric tool based on a possibly invalid theory, it also established the principle that self-report questionnaires, when analyzed using techniques such as factor analysis, can suggest theoretical constructs. It has had particular application in cognitive behavioral therapy (CBT), which aims to challenge and neutralize negative thoughts through techniques such as cognitive restructuring. It was also used as a model for the development of the Kovac's Children Depression Inventory (KCDI).

The BDI was originally developed to provide a quantitative assessment of the intensity of depression. Because it is designed to reflect the depth of depression, it can monitor changes over time and provide an objective measure for judging improvement and the effectiveness or otherwise of treatment methods. The instrument remains widely used in research.

The BDI-II (a 1996 revision of the BDI) was developed in response to the American Psychiatric Association's (APA) publication of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), which changed many of the diagnostic criteria for Major Depressive Disorder (MDD). It is positively correlated with the Hamilton Depression Rating Scale (HDRS) with a Pearson's r-value of 0.71, showing good convergent validity. The test was also shown to have a high one-week test–retest reliability (Pearson's r = 0.93), suggesting that it was not overly sensitive to day-to-day variations in mood. The test also has high internal consistency (α = .91).

Nature of the test

The BDI consists in a 21-question multiple-choice self-report inventory, Its current version (BDI-II) is designed for individuals aged 13 and over. It is composed of items relating to symptoms of depression such as hopelessness and irritability, cognition such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex.

Test score	Depression type
0-13	Minimal
14-19	Mild
20-28	Moderate
29-63	Severe
>/= 64	Most severe

Scoring and interpretation

The standardized cut-off scores are as shown in Table 5:

Table 16.5: Test scores in the Beck Depression Scale II

Limitations

The BDI has the same limitations as other self-report inventories, in that scores can be easily exaggerated or minimized by the person completing them. Like all questionnaires, the way the instrument is administered can also have an effect on the final score. There is no evidence that the BDI-II is more valid or more reliable than other depression scales and public domain scales such as the Patient Health Questionnaire – Nine Item (PHQ-9).

Columbia's Suicide Severity Rating Scale

Test development

The Columbia's Suicide Severity Rating Scale (C-SSRS) is a suicidal ideation and behavior rating scale created by researchers at several universities (Columbia University, University of Pennsylvania, University of Pittsburgh, and New York University). It rates an individual's degree of suicidal ideation on a scale ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent and behaviors."

Questions are phrased for use in an interview format, but the C-SSRS may be completed as a self-report measure if necessary. The scale identifies specific behaviors which may be indicative of an individual's intent to kill oneself. An individual exhibiting even a single behavior identified by the scale was 8 to 10 times more likely to die by suicide.

Patients are asked about:

• Reasons for thinking of suicide;
• General, non-specific thoughts of wanting to end one's life/complete suicide;
• Thoughts of suicide;
• Thought of at least one method during the assessment period;
• Having had active suicidal thoughts of killing oneself;
• Having had any intent to act on such thoughts;
• How frequently have they had these thoughts;
• How long have the thoughts lasted;
• Whether the thoughts can be controlled;
• Any deterrent factors; and
• Any actual, aborted, or interrupted attempt[s];

The C-SSRS has been found to be reliable and valid in the identification of suicide risk in several research studies.

Scoring and interpretation

The Screener contains 6 'yes' or 'no' questions in which respondents are asked to indicate whether they have experienced several thoughts or feelings relating to suicide over the past month and behaviors over their lifetime and past 3 months. Each question addresses a different component of the respondent's suicide ideation severity and behavior (Table 6):

Table 6: Questions in the Columbia's Suicide Severity Rating Scale

An answer of 'yes' to any of the six questions may indicate a need for referral to a trained mental health professional and 'yes' answers to questions 4, 5 or 6 indicate high-risk.

Prevention

People with a known family history of HD may be concerned about whether they may pass the Huntington's gene (HTT) on to their children. They might consider genetic testing and family planning options. If an at-risk parent is considering genetic testing, it can be helpful to meet with a genetic counselor. A genetic counselor explains the potential risks of a positive test result, which may mean that the parent may develop the disease. Also, couples may need to make additional choices about whether to have children or to consider alternatives. They may decide to choose prenatal testing for the gene, preimplantation genetic diagnosis, or in vitro fertilization with donor sperm or eggs. In this latter process, eggs are removed from the ovaries and fertilized with the father's sperm in a laboratory. The embryos are tested for the presence of HTT. Only those testing negative for HTT are implanted in the mother's uterus.

Complications

After HD starts, a person's ability to function gradually gets worse over time. How quickly the disease gets worse and how long it takes vary. The time from the first symptoms to death is often about 10 to 30 years. Juvenile HD usually results in death within 10 to 15 years after symptoms develop.

The depression linked with HD may increase the risk of suicide. Some research suggests that this risk is greater before a diagnosis and also when a person loses independence.

Eventually, a person with HD requires help with all activities of daily living and care. Late in the disease, the person will likely be confined to a bed and unable to speak. Someone with HD is generally able to understand language and has an awareness of family and friends, though some will not recognize family members.

Common causes of death include:

• Pneumonia or other infections.
• Injuries related to falls.
• Complications related to trouble swallowing.

Planning for residential and end-of-life care

HD causes a loss of function and eventually death. It is, therefore, important to plan for care that will be needed

Question #	Nature
1	Wish to be dead.
2	Non-specific suicidal thoughts. If 'yes: answer questions 3-5. If 'no': Skip to question 6.
3-5	More specific suicidal thoughts and intent to act.
6	Suicidal behavior over lifetime and past 3 months.

in the advanced stages of the disease and near the end-of-life. Early discussions about care allow the person with HD to be engaged and to share what they want from their care.

Creating legal documents that define end-of-life care can be helpful to everyone. They empower the person with the disease, and they may prevent conflict among family members as the disease gets worse. Members of the healthcare team can offer advice on the pluses and minuses of care options.

Matters that may need to be addressed include:

- **Care facilities:** In-home nursing care or care in an assisted living facility or nursing home is needed during the advanced stages of the disease.
- **Hospice care:** Hospice services provide care at the end of life that help a person approach death with as little discomfort as possible. This care also provides support and education to family members to help them understand the process of dying.

- **Living wills:** Living wills are legal documents that enable a person to spell out care preferences when it is not possible to make decisions. For example, these directions might say whether or not the person wants life-sustaining interventions or aggressive treatment of an infection.
- **Advance directives:** These legal documents allow one to choose one or more people to make decisions on their behalf. An advance directive may be created for medical decisions or financial matters.

Prognosis

Key pathways

The key pathways are those that affect:

- DNA repair,
- Energy metabolism, and
- Oxidative processes that go on in cells.

These are the pathways that should be emphasized in the search for therapeutics.

Shortening the drug development process

Because of the identification of the above pathways, and assuming the research focus is concentrated thereon, the search for a treatment for HD should be shortened in its development .... but this may take the next few years. In the meantime, some other treatments (drugs, molecules, …) used in other diseases could be repurposed for the present interests. While not perfect, such therapeutics may provide a starting point for the pharmaceutical industry, particularly in trying to design new products that may be even more helpful in the disease. In this effort, fewer, more directed molecules may have a much more relevant assay as the outcome that will speed up the development process.

On future treatments

It is unlikely that treatments will become immediately available to help delay the onset of HD for people who are currently in mid-life, may not have the disease, or may only just beginning to get the disease. For their children, it is likely that better treatments may become available to palliate, but not cure, the disease. Like for other diseases, progress will be incremental.

Fortunately, when compared to Alzheimer's disease (AD), the situation for HD is more favorable because the genetic cause of the disease is known and we can predict with certainty who will be affected. Once the appropriate drugs would have been developed, well powered clinical trials could be carried out.

There are several such initiatives already on their way and cohorts of patients ready for clinical trials when the drugs become available (see Article II in this series)..

Conclusions and take-aways

- To quantify the results of clinical trials, several tests have been developed, including the: Unified Huntington's Disease Rating Scale (UHDRS); Mini-Mental Status Examination; Hodkinson's Abbreviated Mental Test Score (HAMTS); Geriatric Mental State Examination (GMSE); General Practitioner Assessment of Cognition (GPAC); Computerized tests such as CoPs; Mental Attributes Profiling System (MAPS); longer formal tests for deeper analysis of specific deficits; Beck's Depression Inventory (BDI); and the Columbia's Suicide Severity Rating Scale (C-SSRS).

- The UHDR) is a research tool to provide a uniform assessment of the clinical features and course of HD. It is the standard clinical assessment tool in HD. Its key component

descriptors involve a: Motor function, cognitive function, behavioral function, and functional capacity.

- Features of interest of the UHDRS are: A high degree of internal consistency within each of the domains; significant intercorrelations between the domains with the exception of the total behavioral score; and an excellent degree of inter-rater reliability for the motor scores.

- The UHDRS may be useful for tracking changes in the clinical features of HD over time. It appears to be appropriate for repeated administration during clinical studies.

- The MMSE is a widely used test of cognitive function, including tests of orientation, attention, memory, language, and visual-spatial skills. It is used extensively in clinical and research settings to: Measure cognitive impairment; estimate the severity and progression of cognitive impairment; follow the course of cognitive changes in an individual over time; provide a diagnosis for any particular nosological entity; and screen for dementia.

- Advantages to the utilization of the MMSE include: No specialized equipment or training is required for administration; can be customized: is useful for cognitive assessment in the clinician's office space or at the bedside: is valid and reliable for the diagnosis and longitudinal assessment of Alzheimer's disease (AD); and is increasingly reliable in comparisons.

- Disadvantages to the utilization of the MMSE are that it: Is affected by demographic factors: age and education exert the greatest effect; lacks sensitivity to mild cognitive impairment; fails to adequately discriminate patients with mild AD from normal patients; is insensitive to progressive changes occurring with severe AD; and is uncertain at detecting focal lesions.

- The BDI is one of the most widely used psychometric tests for measuring the severity of depression. It was originally developed to provide a quantitative assessment of the intensity of depression. It can monitor changes over time and provide an objective measure for judging improvement and the effectiveness of treatment methods.

- The BDI has the same limitations as other self-report inventories, in that scores can be easily exaggerated or minimized by the person completing them. The way the instrument is administered can also have an effect on the final score.

The C-SSRS is a suicidal ideation and behavior rating scale. It rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan, intent, and behaviors".

- People with a known family history of HD might consider genetic testing and family planning options. Couples may need to make additional choices about whether to have children or to consider alternatives (preimplantation genetic diagnosis, or in vitro fertilization).

- After HD starts, complications arise: a person's ability to function gradually gets worse over time; the depression linked with HD may increase the risk of suicide; eventually, help is requires with all activities of daily living and care.

- Common causes of death include: Pneumonia or other infections, injuries related to falls, complications related to trouble swallowing.

- Planning for residential and end-of-life care will be needed in the advanced stages of the disease and near the end-of-life, including creating legal documents that define end-of-life care. Matters that may need to be addressed include: Care facilities, hospice care, living wills, and advance directives.

- Key pathways to prognosis are those that affect: DNA repair, energy metabolism, and oxidative processes that go on in cells. They should be emphasized in the search for therapeutics.

- Because of the identification of the above pathways, the search for a treatment for HD should be shortened in its development but this may take the next few years. In the meantime, some other treatments (drugs, molecules, ...) used in other diseases could be repurposed for the present interests.

- It is unlikely that treatments will become immediately available to help delay the onset of HD for people who are currently in mid-life, may not have the disease, or may only be just beginning to get the disease. For their children, it is likely that better treatments may become available to palliate, but not cure, the disease. Like for other diseases, progress will be incremental.

- Fortunately, when compared to Alzheimer's disease (AD), the situation for HD is more favorable because the genetic cause of the disease is known and we can predict with certainty who will be affected.

- There are several initiatives already on their way and cohorts of patients ready for clinical trials when the drugs become available.

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