Huntington's disease is a rare, genetic, neurodegenerative disease that has a great impact on patients and families across generations. Huntington's disease affects men and women equally; each child of a parent with HD has a 50/50 chance of inheriting the disease.¹⁻³

Around 1 IN 10,000 people live with Huntington’s disease in the west, with many more potentially at risk.³

Huntington’s disease is a progressive condition characterised by a triad of symptoms including:

Cognitive problems
• Cognitive slowing and problems with planning⁴
• Reduced mental flexibility¹
• Language difficulty²
• Difficulty retrieving new information²
• Working memory impairment³

Behavioural issues
• Depression⁴
• Suicidal behaviour²
• Apathy²
• Irritability⁶
• Aggressive behaviour²

Motor impairment
• Involuntary movements (chorea and dystonia)²,⁴
• Impaired voluntary movement⁴
• Speech difficulty⁴
• Bradykinesia⁶
• Altered balance and gait³
• Abnormal saccadic eye movement⁷

Huntington's disease results in increasing disability, functional decline and loss of independence. Typical adult onset occurs when people are in the prime of life, between 30 and 50 years old.²,⁴

CAG, cytosine, adenine, and guanine; cUHDRS, composite Unified Huntington Disease Rating Scale; IS, Independence Scale; mHTT, mutant huntingtin protein; OLE, open-label extension; SDMT, Symbol Digit Modalities Test; SWR, Stroop Word Reading; TFC, Total Functional Capacity; TMS, Total Motor Score; UHDRS, Unified Huntington Disease Rating Scale.

The cUHDRS assessment includes the four measures most sensitive to Huntington’s disease progression as determined by data from observational studies and placebo arms from interventional studies.¹¹

1.2 points is a clinically meaningful functional decline*.¹²

ASSESSING HUNTINGTON’S DISEASE PROGRESSION

The UHDRS assessment comprises four measures:

- **Motor**
  - Total Motor Score (TMS)

- **Cognitive**
  - Symbol Digit Modalities Test (SDMT)
  - Stroop Word Reading (SWR)
  - Verbal Fluency

- **Behaviour**
  - Behavioural assessment

- **Function**
  - Total Functional Capacity (TFC)
  - Functional Assessment IS

Figure adapted from Ross CA, et al. 2014 and Walker FO. 2007.⁴⁻⁹

* UHDRS score calculation:
  \[
  \text{cUHDRS} = \frac{\text{TFC} - 8.8}{21.2} + \frac{\text{TMS} - 34.4}{12.4} + \frac{\text{SDMT} - 25.2}{2.8} + \frac{\text{SWR} - 58.0}{17.4} + 10^{10}
  \]
In addition to clinical measurement with tools such as cUHDRS, Huntington’s disease can be monitored digitally.13

Tools for digital monitoring can be used to collect data actively or passively:
- Active testing requires patient input and includes traditional tests such as SDMT13
- Passive testing requires the patient to carry devices (usually a smart phone and watch)13

Digital monitoring is a tool that has the potential to provide new insights into Huntington’s disease progression outside the traditional clinical trial setting.14

Huntington’s disease patients live with their condition 365 days a year and therefore assessment of disease progression between clinic visits may potentially enhance disease understanding and lead to better patient care.13–15

The risk of developing Huntington’s disease is associated with the number of CAG repeats in the HTT gene:1,7

<table>
<thead>
<tr>
<th>CAG repeat range</th>
<th>Description of gene</th>
<th>Risk of Huntington’s disease</th>
<th>Risk of Huntington’s disease in next generation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤26</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>27–35</td>
<td>High normal</td>
<td>No</td>
<td>Possible</td>
</tr>
<tr>
<td>36–39</td>
<td>Reduced penetrance</td>
<td>Possible</td>
<td>Yes</td>
</tr>
<tr>
<td>≥40</td>
<td>Full penetrance</td>
<td>Definite</td>
<td>Yes</td>
</tr>
</tbody>
</table>

CAG expansion in the HTT gene results in mutated forms of the huntingtin protein (mHTT).7 mHTT causes neuronal dysfunction and death, resulting in the development of Huntington’s disease symptoms.7 Reducing mHTT protein levels may slow disease progression.7


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