# Development of the Huntington's Disease Integrated Staging System (HD-ISS)

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## Objective

To propose a new HD framework, referred to as the HD-ISS, that comprises an HD biological research definition and evidence-based staging centered on prognostic biological, clinical, and functional landmarks.

## Background

HD is an inherited autosomal dominant neurodegenerative disease. While there is biological certainty that individuals with a pathogenic expansion in the huntingtin gene (*HTT*) will develop the signs and symptoms of HD within a normal lifespan, this is not reflected in presently-used terminology. Current staging methods do not address disease progression before an overt clinical phenotype, despite well-accepted biomarkers of neurodegeneration predating clinical diagnosis. A new research framework is needed to standardize clinical research and enable interventional studies earlier in the course of HD.

## Methods

This framework is the result of a formal consensus process by the HD-RSC's Regulatory Science Forum (RSF), a working group of expert representatives from industry and academia. The RSF considered biomarkers as well as signs and symptoms of the disease to formulate the HD-ISS. Observational data was employed to calculate "cut-offs" using the extreme values in models of the control population to define the HD-ISS Stages and to evaluate the framework.

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## Results

The HD-ISS characterizes individuals based on genetic expansion and allows for common terminology to enable cohesive clinical research and the development of interventional studies on the early phases of HD. The HD-ISS incorporates landmarks demonstrating robust prognostic value to classify individuals into each Stage and data-driven landmark thresholds to define Stage boundaries that are not CAG-dependent. Individual study visits, participant Stage progression, and longitudinal models of Stage progression align with the natural history of HD and with increased CAG predicting accelerated transitions.

We adopted the following definition of HD:

> ***Huntington's disease is defined by the presence of a CAG expansion in exon 1 of the HTT gene of either (a) CAG ≥ 40; or (b) CAG ≥ 36 and the presence of a disease-specific biomarker or disease-specific clinical syndrome***

The temporal sequence of the HD-ISS Stages is conceptualized as follows:

> ***Stage 0: CAG ≥ 40***
> ***Stage 1: CAG ≥ 40 & biomarker of pathogenesis***
> ***Stage 2: CAG ≥ 40 & biomarker of pathogenesis & sign/symptom***
> ***Stage 3: CAG ≥ 40 & biomarker of pathogenesis & sign/symptom & functional change***

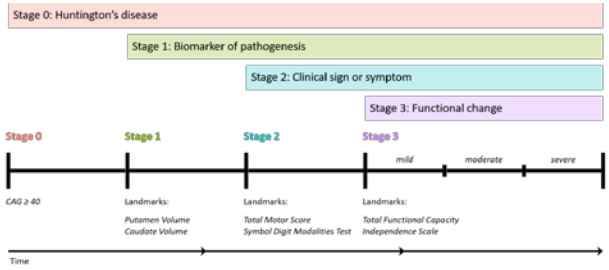


***Figure 1. Cumulative Staging framework and landmarks.*** *(note: time not to scale). Given Stage 3's decades-long duration, we further divided it into three broad conceptual groupings of mild, moderate, and severe functional deficits, defined to give clear boundaries without relying on additional specific quantitative landmarks.*

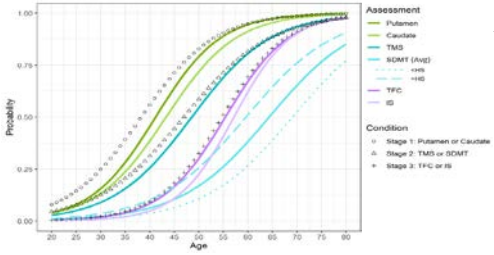


***Figure 2. Assessment and Stage progression curves.*** *Probability of crossing the cut-off for an assessment (lines) and fulfilling the condition (shape) as a function of age. Based on HD individuals with CAG = 42. The SDMT solid line depicts the average probability over education, the SDMT dotted line shows the probability for low education (< than HS education) and the SDMT dashed line shows the probability for high education (> than HS education).*

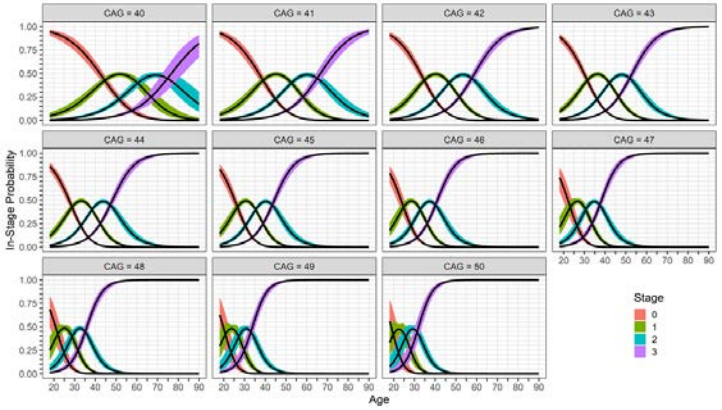


***Figure 3. Stage probability by CAG.*** *The probability of being in a Stage (or in-Stage probability) is plotted as a function of age with a colored ribbon representing the 95% confidence interval. Each panel represents a different CAG length.*

***Figure 4. Overview of the HD-ISS for CAG = 42.*** *Stage probabilities (shaded regions) and the predicted change of the assessments as a proportion of the controls (which maps to a unit scale) as a function of age.*

## Conclusion

The RSF has developed a biological definition of HD and an evidence-based staging system that encompass the full course of the disease and are unconstrained by concepts such as "manifest," "pre-manifest," or "prodromal." The HD-ISS is primarily intended for research settings and provides a new structure to anchor and harmonize clinical study populations and will facilitate assessment of interventions that prevent or delay the onset of HD symptoms. The research use of the HD-ISS will allow for further validation. We hope that the HD-ISS will enable the HD community to work together to change the future of HD.