A new roadmap to track Huntington's disease progression

Researchers have updated the system that classifies Huntington's disease progression. Tracking progression in 4 stages will make clinical trial screening and data interpretation easier and faster, and pave the way for pre-symptomatic trials.

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For those who were following the live tweets from HDBuzz about the CHDI HD Therapeutics Conference or tuned in to the HDSA Convention, we may have caught your attention with the new HD staging system. And if you missed it, you're in luck! The publication detailing this new classification system, how it's used, and its benefits is hot off the press. Let's see what they have to say.

Tracking disease progression – time for an update

Until now, people with Huntington's disease have been categorized primarily based on their clinical symptoms. Physicians watch a patient walk, perform hand movements, or ask them to think of different words. A mix of tests related to thinking, movement, and mood helps medical doctors gauge where individuals are in the course of their disease.

The HD-ISS categorizes Huntington's disease progression on an individual basis using tests that look at brain structure, clinical presentation, and ability to perform day-to-day tasks. Patients progress sequentially through the HD-ISS, from stage 0 through 3.

Diagnosing patients and categorizing their disease stage with clinical symptoms has been going on since the 1800s, long before scientists identified the gene that causes

Huntington's! However, this type of categorization of people with HD is quite dated, and it doesn't always capture the full picture.

Currently, "pre-symptomatic", "prodromal", or "premanifest" patients all fall into a single category. These are individuals who are gene positive for Huntington's but have no clinical signs of the disease – or at least no movement symptoms, which are the most common way HD is diagnosed. This category can include individuals from birth until about the age of 40. This is a huge pool of patients over a long period of time!

As research around Huntington's disease advances, we're learning a lot about very subtle changes that occur even decades before any clinical symptoms are apparent. This has prompted a team of researchers, known as the Huntington's Disease Regulatory Science Consortium (HD-RSC), to develop a more sophisticated scoring system.

How the new system was developed

The Huntington's disease Integrated Staging System – HD-ISS – combines information from brain scans, clinical tests, and day-to-day abilities to determine where HD patients are in their disease. This new scoring system takes into account the entire life of the individual, classifying every age, from birth to death.

To develop this new scoring system, the HD-RSC team used data from the Enroll-HD, TRACK-HD, IMAGE-HD, and PREDICT-HD trials, all observational studies which follow people in HD families over time. A big thank you to everyone who has or is sacrificing their time to participate in these trials – you've made the creation of this new scoring system possible! They also consulted a variety of different groups, including patient advocacy groups.

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HD-ISS stages

In a recent talk to the HD community at the HDSA Convention, Dr. Sarah Tabrizi, who is leading the charge on the HD-ISS, likened the new system to what is used in cancer. Cancer is classified into stages based on the size and spread of the tumor. The HD-ISS will work in a similar way, categorizing patients into 4 stages – stage 0 through 3 from no impairment (birth) through severe impairment (end-of-life). Each stage is sequential, meaning a patient will experience components of the previous stage to be classified into the following stage. The staging system is also progressive, meaning patients will always begin at stage 0 and progress through to stage 3.

Stage 0: HD gene present, no other changes

An individual who has been genetically diagnosed with HD (40 or more CAG repeats), but has no detectable changes associated with Huntington's disease. This stage begins at birth and tracks an individual until they have some sort of detectable change.

Stage 1: HD gene present, biomarker changes only

Individuals move into this stage when there are detectable changes in biomarkers known to occur with Huntington's disease. Based on data from thousands of participants in clinical studies, the biomarkers they chose were the volume of 6 specific areas of the brain using MRI. Changes in these areas are known to decrease in people with HD as cells in the brain are lost.

While the HD-ISS won't come in to play during routine annual visits or affect day-to-day care, it will standardize research and speed clinical trial selection and data interpretation.

Stage 2: HD gene present, biomarker changes, and clinical signs

This stage begins when a patient shows clinical signs of Huntington's disease. The new scale focuses on motor and cognitive changes, as measured with movement tests and a thinking task that asks people to pair numbers with symbols.

Stage 3: HD gene present, biomarker changes, clinical signs, and difficulties with daily function

The last stage begins when a patient experiences functional decline, such as difficulty carrying out day-to-day tasks. Additionally, stage 3 is broken up into mild, moderate, and severe functional decline. Mild stage 3 includes individuals that may take a long time to do routine tasks, but don't require assistance. Moderate stage 3 includes those who require assistance with some routine tasks. Severe stage 3 includes those who require assistance with all routine tasks. The amount of time spent in each disease stage will differ from person-to-person. How quickly an individual progresses through each stage is variable, but strongly depends on age and CAG repeat length.

Why we need the HD-ISS

The HD-ISS will help standardize clinical research by categorizing patients in a more predictable way. This will allow clinicians conducting clinical trials to more quickly select research participants for studies who are likely to have a similar disease course or respond similarly to a treatment. Standardizing the categorization of different stages of Huntington's disease, particularly between birth and the onset of clinical symptoms, is necessary to help the field move toward testing drugs earlier, before clinical symptoms are apparent. Many people think the most effective time to treat HD will be before a person even gets sick, so having a system in place before these trials are designed is critical.

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Also, these clear delineations of patient populations will make it easier for researchers to compare data across studies – something that has been a bit muddy in the past because of loose definitions of disease stage. Comparing data across studies will allow researchers to gain as much information as possible from each trial, which will decrease the amount of time it takes to get to our end goal – a treatment for HD.

How will the HD-ISS affect research and care?

It's important to note that the HD-ISS is focused on research - it aims to streamline the design and recruitment of clinical trials. This newly published system doesn't mean that doctors who treat HD will suddenly be categorizing their patients. In fact, that's not necessary to develop an individualized treatment plan based on a person's current symptoms. But once therapies to slow disease progression become available, the system could help guide treatment decisions.

Another key message is that a more rigorous system for trial selection doesn't mean the therapies being tested couldn't benefit others in a different stage of HD. This is first and foremost a way to make trials smoother and data easier to interpret, which has the potential to speed the drug pipeline by leaps and bounds.

Implementation of the new HD-ISS scoring system should be straightforward for the Huntington's community. In fact, the upcoming PTC Therapeutics trial for PTC-518 will be the first to use the HD-ISS. Most of the measurements collected for this staging system, like CAG repeat length, brain imaging, and functional capacity scores, are standard in Huntington's disease research. Standardizing the way various stages of Huntington's disease are classified is a clinical advancement that will help organize trial selection and data interpretation as we advance toward treatments for HD.

The authors have no conflicts of interest to declare.For more information about our

disclosure policy see our FAQ...

GLOSSARY

observational A study in which measurements are made in human volunteers but no experimental drug or treatment is given

therapeutics treatments

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

biomarker a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

prodromal prior to onset or diagnosis of movement symptoms

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

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