

Preparing for Preventive Clinical Trials: The Predict-HD Study

Lisa J. Bain – June 2007

In the first published report emanating from The Predict-HD study¹, several markers of HD were shown to appear long before an individual would expect to be diagnosed. More importantly, since the markers varied in measurable and predictable ways prior to diagnosis, they may prove useful in upcoming clinical trials to determine whether experimental treatments can slow the progression of the disease.

Who took part in this study?

Dr. Jane Paulsen from the University of Iowa led a team of over 100 investigators from 24 sites across the United States, Canada, and Australia. The study enrolled 505 people at risk for HD who had already undergone genetic testing but who had not been clinically diagnosed with the disease.

What did the participants do?

Participants in the study were examined by HD-knowledgeable clinicians and also gave blood and received imaging studies and neuropsychological evaluations. The goal of the research project was to look for signs, or markers, of HD that might appear before diagnosis, whether those markers showed up as something that could be measured in the blood, could be seen in a magnetic resonance image (MRI), or could be picked up with tests of a person's memory or ability to learn or perform certain tasks.

What did the researchers do?

Using the age and **CAG repeat length** for each of the participants, the researchers used a formula to estimate when the person was likely to show motor symptoms that could lead to a diagnosis of HD. Meanwhile, clinicians rated each person according to their motor performance as having no signs of HD, "soft" signs of HD, possible HD, or probable HD; and other clinicians rated the cognitive performance and psychiatric distress of the volunteers. MRIs were used to measure the volume of the area of the brain called the striatum that has been shown to be most affected in people with HD. The raters were unaware of the person's CAG repeat length at the time of their examinations.

What did they learn?

When all the data were collected and analyzed together, they showed that as people got closer to their expected time of onset, their brain volumes decreased and they performed more poorly on motor tests as well as on tests of memory and learning. There was also a high rate of depression among the participants in this study, particularly among those who were closer to diagnosis.

Why is this study important?

This study shows more clearly than ever before that the brains of people with HD are affected long before symptoms appear, and that therefore, treatment must also begin before the disease becomes apparent. As the study continues, the researchers will be

gathering more data on how these various disease markers progress, so that when preventive treatments become available, they can use these markers to show whether a treatment is having a beneficial effect on the disease. Having measurable markers like this allows researchers to measure the effectiveness of a treatment using a smaller number of subjects, so this should speed up and reduce the cost of conducting clinical trials.

This study will also show whether the formula that researchers use to estimate when a person is likely to develop symptoms is, in fact, accurate.

Were there any surprises in this study?

According to Dr. Martha Nance, a neurologist who helped plan the study and also took part as a clinical investigator, “the first big surprise, and it was a wonderful surprise, was how incredibly willing people were to be involved in the study.” Since only a minority of people who are at risk of HD have undergone genetic testing, which is required for this study, the pool of potential participants was small to begin with. Moreover, volunteering for a clinical trial such as this involves not only a significant time commitment, but also requires people who are at risk for HD but have no symptoms to reconfront the disease every year when they come for follow-up visits; and many people prefer not to think about it. In addition some at-risk individuals fear that their privacy will be compromised. Despite these concerns, however, Dr. Nance said that people who volunteer “understand that this is a unique thing they can do to really help us break some barriers.”

Dr. Nance said that the study also revealed the value of MRI and the importance of having careful measurements made by experts. Prior to this study, she said she had always told medical students and patients that MRI results lag behind clinical findings, but this study showed “how much information you lose when you look at a scan with your eyeballs,” rather than with calipers and careful measurements.

“I wonder if it will revolutionize how people read MRI scans,” she said.

What’s next?

The current publication reports only the results of participants’ initial exams, but it will be important to follow people over time to see how symptoms progress. The National Institutes of Health (NIH) initially funded the study for five years, but the researchers hope that additional funding will be found so that they can continue to follow participants over a longer period of time. The study should also provide valuable information about the transition from pre-symptomatic to symptomatic, which will help patients, their families, and clinicians learn what can be done to alleviate problems during this critical period.

CAG repeat length : CAG stands for the three nucleotides (DNA building blocks), Cytosine, Adenine, and Guanine. The Huntington mutation consists of multiple repeats of CAG in the DNA. Fewer than 30 repeats is considered normal, whereas more than 39 repeats means the person will develop HD.

¹ Arch Neurol. 2006; 63:883-890.