

At Risk for Huntington Disease: The PHAROS Cohort Enrolled

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July 2007

Among the 150,000 or so individuals in the United States and Canada who are at risk for Huntington disease (HD), only a fraction have chosen to undergo genetic testing that would tell them if, in fact, they have the HD gene. Since people who have decided against genetic testing make up the majority of people at risk for HD, a group of Huntington Study Group investigators reasoned that studying this group might provide critical information about the earliest indicators of the disease. Thus, these investigators designed the Prospective Huntington At Risk Observational Study (PHAROS), and in July, 2006, they published the first report from that study¹, which described the characteristics of the participants at the beginning of the trial (baseline).

Who took part in this study?

Investigators at 43 sites in the United States and Canada began screening, enrolling, and evaluating participants in 1999. Over the next 4 ½ years, 1001 people were enrolled. In order to qualify, participants had to be unaffected but at a 50-50 chance of developing HD by virtue of having an affected parent or sibling. Only people between the ages of 26 and 55 were included, since they would have the greatest risk of developing HD over the study period. None had undergone genetic testing. Dr. Ira Shoulson, Principal Investigator for the PHAROS study and a neurologist at the University of Rochester said that one of the things learned from this study was that these individuals who reject genetic testing are nonetheless willing to participate in research that may benefit them or their families.

What did the participants do?

Participants consented to participate in this study only after being assured that their privacy would be protected and no genetic or clinical information would be disclosed to anyone. They agreed to undergo repeated clinical examinations approximately every 9 months for a minimum of 4 years. At each visit, they had a physical examination and neuropsychological testing, completed several questionnaires, and provided a medical history. They also provided a blood sample, which was used to determine their genetic status and also to look for possible biomarkers of the disease. Neither the participants nor the examiners were told the results of the genetic testing. If a participant changes her (or his) mind during the course of the study and wants to know her genetic status, she is referred for comprehensive genetic counseling and asked not to reveal the results to the PHAROS researchers.

What did the researchers do?

Before starting the trial, the investigators worked extensively with the regulatory groups at their home institutions as well as the National Institutes of Health (NIH), which funded the study, to design protocols that would protect the participants' privacy. Since these participants had made the decision that they did not wish to know if they would eventually develop HD, the investigators designed elaborate systems to prevent the disclosure of any clinical or genetic information. After enrolling participants, the investigators collect motor, cognitive, and behavioral data at each examination, which they will use to determine if, over the study period, participants begin to develop signs of HD, and what those earliest signs are.

What did they learn?

About twice as many women as men volunteered to participate in this study despite attempts to recruit more men. Dr. Shoulson said that this is in line with what other observational studies have shown, and suggests that women may be more altruistic than men in their willingness to participate in research that is unlikely to have any direct or immediate benefit. Generally, the participants were highly educated and working; and only a few said they had symptoms that might be related to HD. Baseline assessments confirmed that most of the participants had few signs of HD, either motor, cognitive, or behavioral. An independent rater at each study site performed the motor examinations and assigned a “diagnostic confidence of HD” rating. At baseline, 92.3% of the participants received a rating of 0 or 1, meaning that they had no or nonspecific motor abnormalities. Another 6.7% received a rating of 2 or 3, indicating motor abnormalities that might be, or were likely, signs of HD. Only 1 % received a rating of 4, meaning that they had definite signs of HD.

Why is this study important?

This study, like the [PREDICT study](#) should provide information about the earliest clinical features of HD, which will be useful in determining who should be enrolled in clinical treatment trials, and when treatment should begin. In addition, this group of individuals who have chosen not to know if they have the HD gene may help clarify whether some of the early signs that people report, anxiety for example, are specific to HD or a result of knowing you are at risk. Another important outcome of this study will be a better understanding of the attitudes and beliefs of people at risk for HD. Dr. Kimberly Quaid, a member of the steering committee and professor of medicine at the Indiana University School of Medicine, led a group that conducted an interview study with a subset of PHAROS participants to examine the experiences of people living with the risk of developing HD. This study, which has not yet been published, explored ideas related to the decision about whether to have genetic testing, the consequences of living with uncertainty, and the importance of hope.

Were there any roadblocks or surprises encountered with this study?

Retention in the study has been high, and according to Dr. Shoulson, some people who withdrew subsequently decided to return, which was a pleasant surprise. “I do not think we had any roadblocks,” he said, “But all of us were mindful of the fact that we were working in uncharted territory.” Both investigators and the NIH were preoccupied with protecting confidentiality and privacy, and a great deal of effort was put into these aspects of the design. In retrospect, Dr. Shoulson said he thinks the investigators overprotected, and did not communicate enough with the participants. That turned out to be a mistake, which required an adjustment of the consent process. Now, the PHAROS investigators produce a newsletter to keep participants informed and involved. “The research participants love that,” said Dr. Shoulson.

What's next?

Data collection continues. Statistical analyses that were done prior to launching the trial estimated that about 4 in 10 of the enrolled subjects would have the gene and that fewer than 100 would begin to show signs of HD during the 4-year study period. Since the NIH recently agreed to extend funding for this study for an additional three years, it is likely that a larger number of participants will begin to show early signs of HD, adding to the power of the study and providing information that will help in the design of treatment trials for new drugs that are in the pipeline.

¹ The Huntington Study Group PHAROS Investigators. At Risk for Huntington Disease: The PHAROS (Prospective Huntington At Risk Observational Study) Cohort Enrolled. 2006 Arch Neurol 63:991.