

Huntington Study Group (HSG) Policy on Non-Disclosure of CAG Trinucleotide Repeat Length (CAGn) Genetic (DNA) Information

as formulated by the HSG Committee of Michael Conneally, Kimberly Quaid, Nancy Wexler and the HSG Executive Committee (Anne Young, John Penney, Dennis Choi, Karl Kiebertz, David Oakes, Ira Shoulson, Chair) and as reviewed and approved by the HSG members (December 3, 1994 and February 13, 1995).

Background:

Identification of the Huntington's disease (HD) gene in 1993 has led to the relatively wide availability of DNA testing for persons at risk for HD and in selected cases for symptomatic individuals to confirm the diagnosis. The testing involves and amplification and counting of the repetitive length of cytosine-adenine-guanine trinucleotides (CAGn) within the region of the HD gene.

While CAGn greater than 38 repeats confers high probability (~ 99%) for carrying the HD gene, the ranges of CAGn for "indeterminate" and "low probability" of HD gene carrier status have not been firmly established. Although there is a statistical correlation (inverse) between CAGn and the age at onset of HD, much of this correlation is accounted for by juvenile-onset individuals who have 60 or more CAGn. Moreover, CAGn only accounts for about 50% of the variance of age at onset and has not been found to correlate consistently with the clinical features or progression of HD. The variability of CAGn between testing laboratories has also not been examined systematically.

HSG Clinical Research Studies:

The therapeutic trials and other clinical research studies of the Huntington Study Group (HSG) provide a rich opportunity to confidently determine the relationship, if any, between CAGn and the clinical expression of HD. Since the clinical measures of HD are largely subjective and depend upon an examiner's evaluation, knowledge of CAGn may introduce bias in clinical assessments. This issue is of particular concern in research studies where such bias may contribute to misleading results and interpretations. A dispassionate assessment of CAGn and clinical features is essential in clarifying the predictability of CAGn for the onset, characteristics and course of HD.

HSG Resolution:

On December 3, 1994, the members of the HSG convened in Baltimore, Maryland to discuss CAGn and related issues. By an overwhelming vote, the investigators of the HSG adopted the following resolution:

- In the event that CAGn testing is required for individuals who have or are suspected of having HD, either for clinical or research purposes, then the CAGn results should be reported (to the individual, family and clinician) only as one of three categories:
 - CAGn within the normal (low probability) range,
 - CAGn within the indeterminate range, or
 - CAGn consistent with the diagnosis of HD (high probability).

- By providing appropriate consent, individuals with clinical features of HD who undergo CAGn testing should acknowledge that they will be provided information only regarding one of these three categories and not information about the exact number of CAGn.
- Clinicians should also not be informed about the exact number of CAGn. In order to help ensure adequate quality control of CAGn reporting, research sites may wish to designate a professional who can verify the exact CAGn and confirm that the specific laboratory report of CAGn testing is accurate and meaningful. However, such an individual should be excluded from participating as an investigator (examiner) in clinical research studies and should not communicate the exact number of CAGn to the person tested, family, or clinicians.

The range of CAGn corresponding to the foregoing categories (high probability of HD, indeterminate, low probability of HD) has not yet been established. However, the collective experience among HSG testing sites, using a conservative categorization, approximates the following ranges:

CAGn	Category of Results
38 or greater	high probability of HD
30-37	indeterminate
29 or fewer	low probability of HD

This categorization is tentative and primarily relevant to clinical research studies involving (symptomatic) individuals with clinical features of HD. To minimize false-positive diagnosis, more conservative ranges might be applicable for (asymptomatic) at-risk individuals (e.g., 40 or greater for high probability, 30-39 for indeterminate).

In order to maintain the integrity of clinical research studies involving correlation of CAGn, it is important that all examiners (investigators) remain unaware (blinded) to the exact number of CAGn of the research participants. In studies involving individuals who have a family history and clinical features characteristic of HD, the exact number of CAGn need not be disclosed to the investigator or to the patient (or family). Such non-disclosure of CAGn maximizes the likelihood that accurate and meaningful clinical-CAGn correlations will be established. In the event that patients have been made aware of the exact number of their CAGn, this information should not be divulged to clinical investigators.

These guidelines apply particularly to clinical research studies of the HSG, including controlled investigations of experimental drugs. HD individuals who have been informed of their number of CAGn will not be excluded from HSG studies merely on the basis of such a disclosure. However, every effort should be made by the potential research participants, families and investigators to prevent or minimize the disclosure of such information.

This policy pertains primarily to persons with manifest of suspected HD since the HSG is not currently conducting studies involving persons at risk for HD. However, it could be reasonably argued that asymptomatic persons at risk for HD who undergo CAGn testing should only be informed of the category of results and not the specific number of CAG.

Variability in CAGn Between Laboratories:

The potential variability of CAGn analyses and reporting between testing laboratories has not been systematically examined. Such data would obviously have bearing on the categorization of CAGn as well as on the reliability of CAGn for clinical testing. To address this lack of knowledge, the HSG is carrying out a research study to examine the potential variability of CAGn among four research laboratories. The data from this controlled study, involving 60 to 70 research participants, should be available by the end of 1995.

Summary:

The HSG has developed research guidelines to minimize the disclosure of CAGn for their clinical research studies. Tentative categories CAGn have been formulated. Studies are underway to examine the validity and reliability of CAGn with respect to the clinical features of HD and between testing laboratories. The HSG is committed to an ongoing reassessment of these policies in an effort to obtain an unbiased examination of CAGn and its correlates.