

Genetic Testing

The science and practice of genetic testing for Huntington's disease

Individuals at risk for Huntington's disease (HD) have the option of undergoing genetic testing, which detects the presence or absence of the genetic sequence that causes HD. The decision of whether or not to undergo genetic testing is intensely personal, with many factors to consider. This chapter will provide scientific background information regarding genetic testing for Huntington's disease.

- [How is genetic testing for HD possible?](#)
- [Are there guidelines for genetic testing?](#)
- [Who is at risk for HD?](#)
- [When is an individual tested for HD?](#)
- [Where does genetic testing occur?](#)
- [What are the preliminary steps of the genetic testing process?](#)
- [What does the actual genetic test entail?](#)
- [What are the possible test results?](#)
- [How accurate is the genetic test for HD?](#)
- [Are genetic test results confidential?](#)
- [What are the potential consequences of genetic testing?](#)
- [What if I decide not to be tested?](#)

Genetic Testing Part 1

The science and practice of testing for Huntington's disease

How is genetic testing for HD possible?

In 1983, a team of scientists located the first genetic [marker](#) for Huntington's disease, indicating the approximate location of the [Huntington gene](#) on [chromosome 4](#). This discovery led to the development of the first [pre-symptomatic](#) genetic test for HD, which traced the inheritance of markers linked to the Huntington gene. This original test procedure required blood samples from several family members and was not widely available or informative in all cases.

In 1993, the Huntington's Disease Collaborative Research Group isolated the [Huntington gene](#) and identified the [hereditary](#) version of this gene that causes HD. They discovered

that in all people, the three-letter [codon](#) sequence C-A-G is repeated several times at one end of the Huntington gene. In people with HD, the Huntington gene contains an increased number of CAG repeats. Thus, there are different versions, or [alleles](#), of the Huntington gene. (Within this website, any allele within the normal range of CAG repeats is referred to as a “[non-HD allele](#),” and any allele with extra CAG repeats is described as an “[HD allele](#).”) The HD allele produces a longer than usual huntingtin protein, which in turn leads to HD. (For more information about the Huntington gene and altered huntingtin protein, click [here](#).)

The discovery of the [genetic](#) variant that is responsible for HD allowed for the development of a highly accurate direct gene test for HD that is the subject of this chapter.

Genetic Testing

Part 2

The science and practice of testing for Huntington's disease

Are there guidelines for genetic testing?

Although complex ethical and practical concerns surround the practice of genetic testing, there are no national laws regarding predictive testing for HD. In the absence of any official or enforceable regulations, guidelines for genetic testing have been developed by the Huntington’s Disease Society of America (HDSA), the Huntington’s Disease Society of Canada, and the International Huntington Association, in conjunction with the World Federation of Neurology Research Group on Huntington’s Chorea. These guidelines are integrated within the information of this chapter. For a complete list of guidelines, click [here](#).

Genetic testing guidelines stress that the decision to undergo genetic testing should only be made under informed consent, ensuring that the individual being tested fully understands the risks and benefits of genetic testing and can make an independent decision. Further, an individual should be able to withdraw from testing at any time. The guidelines also outline specific steps for genetic testing, emphasizing the importance of counseling throughout the entire process. (To read about the steps of the genetic testing process, click [here](#)) In addition to general guidelines, laboratory guidelines for genetic testing have been developed by the American College of Medical Genetics and the American Society of Human Genetics. These recommendations call for a standardization of laboratory methods, procedures, and terminology.

Genetic Testing

Part 3

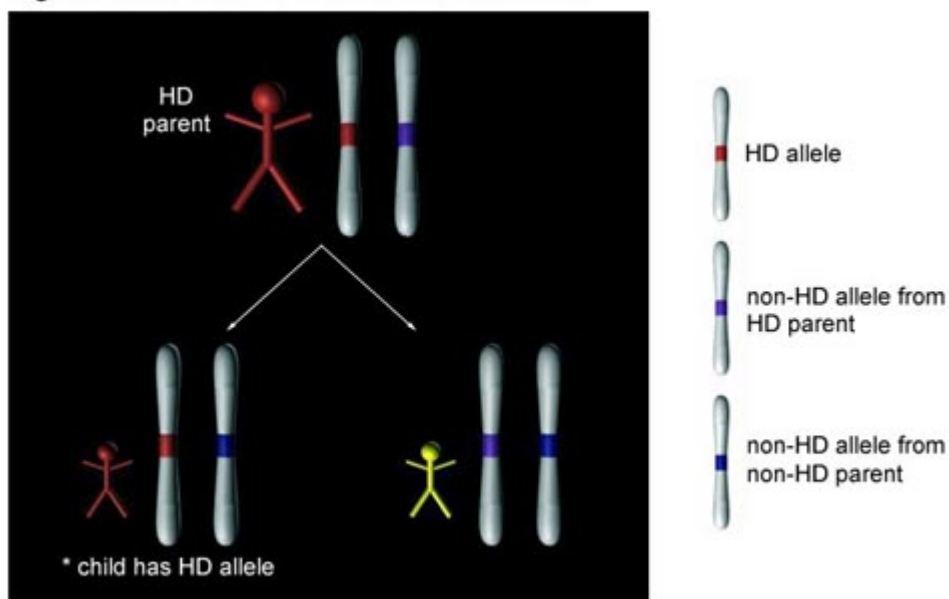
The science and practice of testing for Huntington's disease

Who is at risk for HD?

HD is a [hereditary](#) disorder, meaning that it is passed on genetically through generations. Thus, in almost all cases, there must be a family history of HD in order for one to be at risk for developing the disorder. (Exceptional cases may be if family members who had the HD allele died at an early age before symptoms appeared, or if they were misdiagnosed as having another disorder with HD-like symptoms. Also, although very rare, cases of new [mutations](#) have been documented).

HD is inherited in an [autosomal dominant](#) pattern, meaning that inheriting only one copy of the HD allele from a parent is sufficient to cause an individual to develop HD. Thus, a child who has one affected parent has a 50% risk of inheriting the mutated version of the Huntington gene and eventually developing HD. In reality, this “50% risk” reflects the equal probabilities that either the individual carries the HD allele and will develop HD; or, that the individual has all non-HD alleles and will not develop HD.

Figure C-2: Risk for child of HD individual



Each child has 1 in 2 chance of inheriting the non-HD allele. This is a 50% risk.

Thus, the most common candidate for genetic testing is an adult whose parent has the HD allele or is at risk for having the HD allele. Other cases of genetic testing are discussed in the next section, Part 4. For a more in-depth explanation of the inheritance of HD, click [here](#).

Genetic Testing

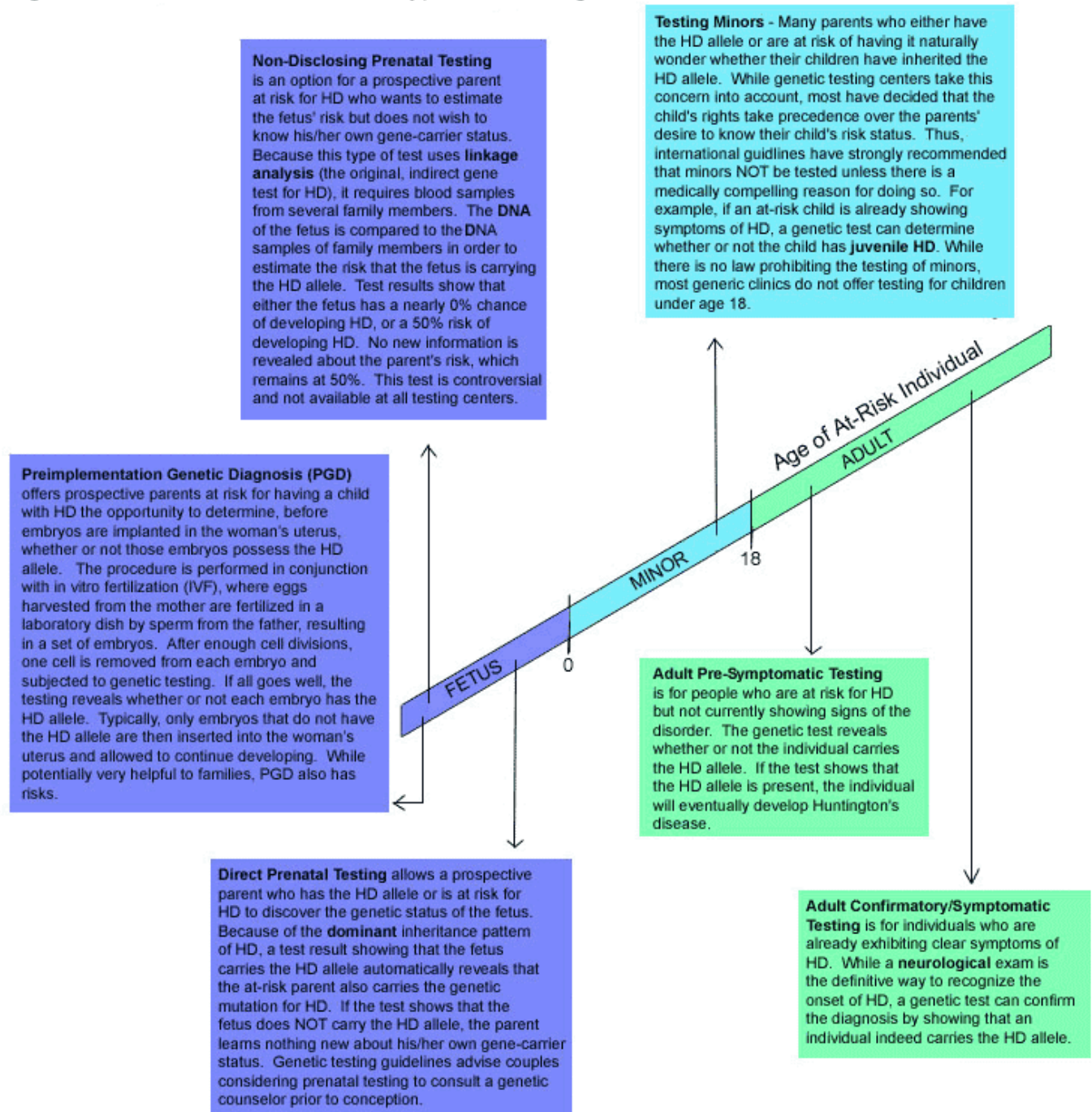
Part 4

The science and practice of testing for Huntington's disease

When is an individual tested for HD?

Technically, the genetic test for HD can be performed on an individual of any age, even an [embryo](#). There are several categories of testing based on when the test is administered:

Figure S-1: Timeline of Different Types of Testing



For more information on Preimplantation genetic diagnosis (PGD), visit: www.preimplantationgenetictesting.com.

Genetic Testing Part 5

Where does genetic testing occur?

There are over 75 established Huntington's disease testing centers across the country. At these genetic clinics, neurologists, genetic counselors, psychiatrists, and psychologists guide an individual through the genetic testing process. Many of these centers are associated with state universities, while others are affiliated with private hospitals and clinics. Each center has its own guidelines regarding specific testing procedures and policies. The Huntington's Disease Society of America (HDSA) publishes a complete list of testing centers.

Genetic Testing

Part 6

The science and practice of testing for Huntington's disease

What are the preliminary steps of the genetic testing process?

Although specific procedures vary among testing centers, genetic testing for Huntington's disease generally involves several sessions that take place over the period of at least one month.

Step 1: Pre-test Genetic Counseling

A genetic counselor provides the individual who is considering testing with basic background knowledge about genetics, the inheritance of HD, and the testing procedure. These preliminary sessions ensure that the individual understands the clinical and psychological implications of genetic testing and is prepared to receive the test results.

Step 2: Neurological Examination

The purpose of this clinical phase is to determine whether the at-risk individual is already showing [symptoms](#) of HD. A [neurologist](#) tests body movement, reflexes, eye movement, hearing, and balance. Brain imaging scans may also be used to check for the characteristic changes in brain structure caused by HD. These clinical observations are combined with an extensive family medical history in order to yield the diagnosis. If an

individual is found to be symptomatic, he/ she can either continue with the genetic testing process to confirm the diagnosis, or withdraw from genetic testing.

What is the difference between testing for HD and diagnosing HD?

Genetic testing shows whether or not an individual carries the HD allele, a mutated version of the Huntington gene. A positive test result indicates that the HD allele is present and that the individual will eventually develop Huntington's disease. However, the genetic test is not sufficient to [diagnose](#) HD because it does not show whether the clinical [symptoms](#) are already being expressed. This information can only be obtained through the neurological exam discussed above, which is the definitive means of diagnosing or establishing the onset of HD.

Step 3: Psychological/Psychiatric Interview

In this phase, a mental health professional assesses the mental and emotional state of the individual considering testing and provides counseling support services.

Generally, there is a time interval between the preliminary sessions and the actual genetic test. This waiting period provides the individual with sufficient time to consider the implications of genetic testing and reach a final decision.

Genetic Testing Part 7

The science and practice of testing for Huntington's disease

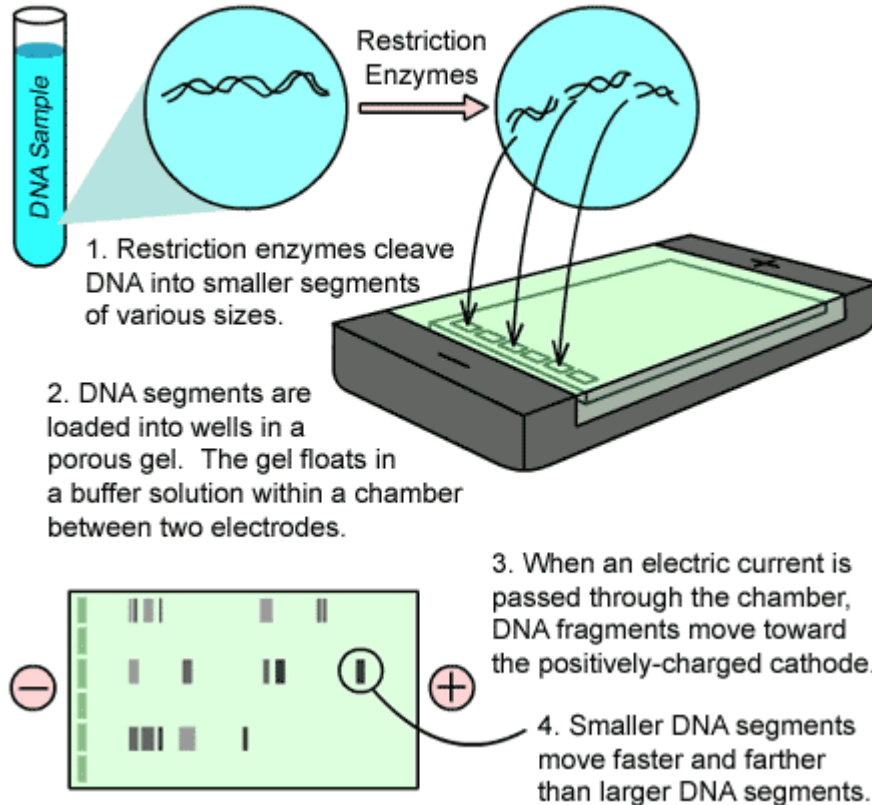
What does the actual test entail?

The genetic test itself is simply a blood test, in which a small sample of blood is drawn from the individual being tested. Technically, it is unnecessary to obtain blood samples from other family members, (except in the case of the non-disclosing prenatal test discussed in Part 4). However, testing centers may request a blood sample, genetic test results, or the medical records of a family member who has HD in order to confirm the diagnosis of HD in the family. In prenatal testing, DNA samples are obtained from the fetus by [chorionic villus sampling \(CVS\)](#) or [amniocentesis](#).

The blood sample is then sent to a laboratory where DNA testing is performed to check for the expanded CAG repeat (To learn more about expansions and mutations, click [here](#).) within the [Huntington gene](#). DNA is isolated from the blood sample and amplified through the [polymerase chain reaction \(PCR\)](#), a technique for rapidly producing millions

of copies of a particular stretch of DNA. In this case, PCR is used to amplify the region of DNA containing the Huntington gene, allowing for closer study.

Figure S-2: Gel Electrophoresis



The size of the CAG repeat can then be assessed through [gel electrophoresis](#). First, [restriction enzymes](#) cleave the DNA into even smaller segments of various sizes. These fragments are placed in a porous gel that floats in a salty buffer solution, in a chamber between two electrodes. An electric current is passed through the chamber, causing the negatively charged DNA molecules to begin migrating through the gel, toward the positively charged electrode. The DNA segments become separated throughout the gel based on their size, as smaller fragments move through the gel “sieve” faster than larger fragments. Then, the separated DNA fragments can be examined individually and “counted,” indicating the number of CAG repeats in the Huntington gene. This number determines whether or not the individual will develop HD.

Genetic Testing Part 8

The science and practice of testing for Huntington's disease

What are the possible test results?

Test results are generally disclosed in person by a genetic counselor. The participant has a right to decide before the delivery of results to not receive this information. Individuals who do return to the testing center receive one of three possible test results:

A NEGATIVE test result:

If the CAG repeat size is found to be in the normal range (less than 35 repeats), then the individual does not carry the genetic mutation for Huntington's disease and is not at risk for developing the disorder.

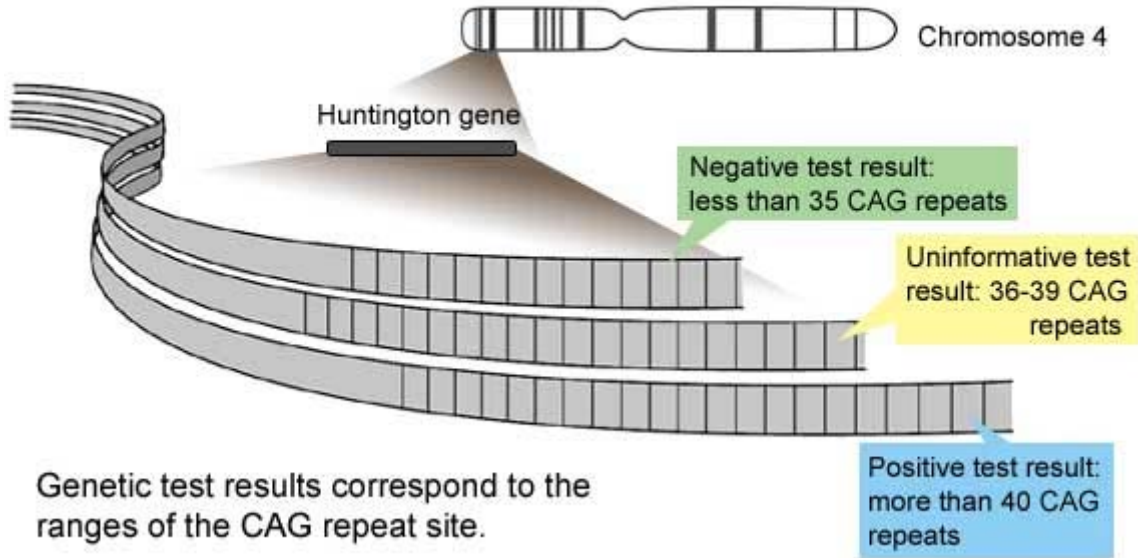
A POSITIVE test result:

If the Huntington gene contains 40 or more CAG repeats, then the individual carries the HD allele and will eventually develop Huntington's disease. A positive test result provides little, if any, information about what to expect in terms of the age of onset, the rate of progression, or the severity of symptoms of HD. Although there is a statistical association between a greater number of CAG repeats and earlier age at onset, variability in this relationship can prevent repeat length from accurately predicting age at onset.

An UNINFORMATIVE test result:

If the CAG repeat length is in the intermediate range (36-39 repeats), it is unclear whether or not the individual will develop HD. Only 1-4% of people tested for HD receive this inconclusive result. Further research may provide more information about the significance of this intermediate number of CAG repeats.

Figure S-3: CAG Repeat Counts on the Huntington gene



Receiving any one of these three test results carries intense clinical and psychological implications. Thus, genetic testing is generally followed by regularly scheduled post-test counseling sessions.

Genetic Testing Part 9

The science and practice of testing for Huntington's disease

How accurate is the genetic test for HD?

A positive or negative genetic test result for HD is 98-99% accurate. The genetic test is not absolutely 100% accurate because of the possibility of human or technical error that is unavoidable in laboratory procedures. A test result that shows an intermediate range of CAG repeats does not show whether or not an individual will develop HD. If an individual requests, repeat testing can sometimes be performed in order to confirm the accuracy of test results.

Genetic Testing Part 10

The science and practice of testing for Huntington's disease

Are genetic test results confidential?

Generally, all information obtained through genetic testing is strictly confidential. According to guidelines for genetic testing, test results should not be disclosed to anyone other than the individual who was tested, unless that individual gives his/ her written consent. However, individual state laws govern professional-patient confidentiality, and the specifics of these laws vary from state to state. Thus, individuals considering genetic testing should become familiar with the laws of the state in which they will be tested and the specific policies of their testing center. In some cases, an individual can increase the confidentiality of his/her test results by requesting that they be classified in a psychiatric record instead of in a general medical record.

Technically, it is possible to perform a direct genetic test for HD on an anonymous blood sample. However, genetic testing guidelines advise laboratories NOT to accept anonymous blood samples for HD testing. According to the Huntington's Disease Society of America's *Guidelines for Genetic Testing for Huntington's Disease*, "While the confidentiality of genetic test results is of great concern, anonymous testing would not increase the protection for a person at risk for Huntington's disease and could pose a danger." Thus, anonymous genetic testing for HD is generally not available at official genetic testing centers.

Genetic Testing

Part 11

The science and practice of testing for Huntington's disease

What are the potential consequences of genetic testing?

Individuals undergoing a blood test may experience discomfort from the needle prick and may develop a small bruise at the site of blood withdrawal. Aside from these minor physical risks, people considering genetic testing are often concerned with other potential consequences such as difficulties with confidentiality, genetic discrimination in employment or insurance coverage, and how the test results may affect family dynamics or personal relationships. These are valid concerns that warrant much consideration and discussion. However, these topics will not be discussed here because they touch on issues beyond the scope of this website, which focuses on providing scientific information about HD. Many resources are available for information on these issues through genetic testing centers, Huntington's disease organizations and literature, and local support groups. For

information from the Huntington's Disease Advocacy Center (HDAC) on political issues related to HD, click [here](#).

Genetic Testing

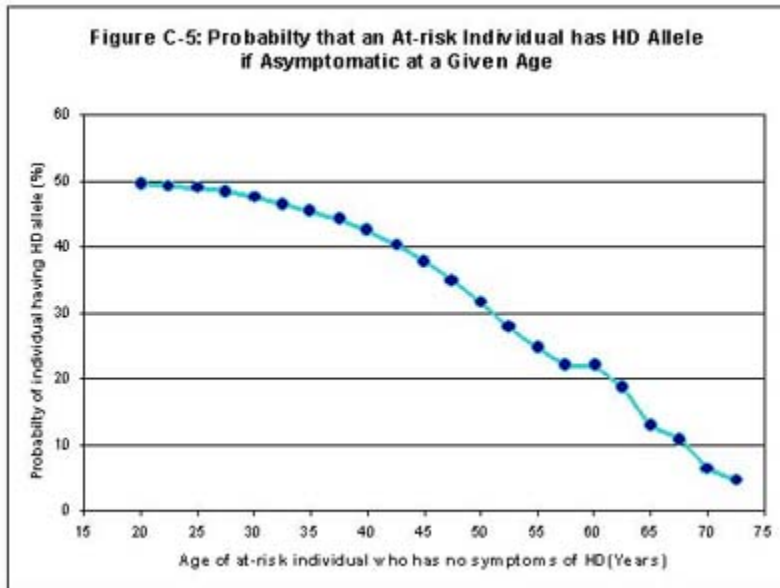
Part 12

The science and practice of testing for Huntington's disease

What if I decide not to be tested?

Many individuals decide that they would rather live at risk than discover that they have an HD allele. For some, the chances of experiencing the relief of having no HD-alleles are outweighed by the risk of finding out the opposite - that if they live long enough they are very likely to develop symptoms of HD. The decision to be tested is a personal choice and should be approached very carefully. Counseling during and after the testing process is an essential part of preparing the individual for the potentially life-changing test results they will receive. It is common even for those individuals who learn that they do not have an HD-allele to experience high levels of anxiety after learning their results. Hence, the process is intentionally designed to give the people involved plenty of time to rethink their decision. Many individuals choose to be tested but never return to hear the results.

So what happens if you choose to live at-risk, without undergoing testing? Most individuals with the HD allele develop symptoms during the third, fourth, and fifth decades of life. A smaller percentage of individuals develop HD in their 60's and afterwards. [Figure C-5](#) lists the probability that you have the HD allele if you are 50% at-risk and remain asymptomatic at a given age. These data were compiled by taking all the at-risk individuals in a specific age group who show no symptoms (are asymptomatic) and then calculating the percentage of these individuals that developed HD later in life. For example, of the individuals who were asymptomatic at age 50 years, 31.5% developed HD at some later age.



This figure pertains to at-risk individuals - those who have a parent with HD - and therefore assumes a 50% probability of actually inheriting the HD allele. However, as one gets older and remains asymptomatic, the *odds* of having the allele decrease (as implied by the graph). This pattern arises because most individuals with the allele will already have developed HD by a given age. If a person has already lived a certain number of years without developing symptoms, then chances are relatively high that this person may be in the group that does not have the allele. Conversely, chances are lower that this person is in the group that does have the HD allele. *Please note: the information in this graph is not, in any way, a substitute for a genetic test.* The numbers do not represent exact predictions for the probability that an individual who is asymptomatic at a given age will develop HD later in life. However, the figure gives a rough estimate of how this probability changes over the course of a lifetime.

-C. Barnard 7-24-02 (Parts 1-11)

-A. Hsu 9-10-01 (Part 12)

For further reading:

1. Genzyme Corporation. "Huntington's Disease." Sept. 5, 2001. www.genzyme.com/genetics/clinicalinfo/molgen/huntington.htm
2. Hersch S, et al. "The Neurogenetics Genie: Testing for the Huntington's Disease Mutation." *Neurology* 44.8 (1994): 1369-1373.
3. Huntington's Disease Society of America, Inc. "Guidelines for Genetic Testing for Huntington's Disease." (1994).
4. Huntington's Disease Society of America, Inc. "Genetic Testing for Huntington's Disease: A Guide for Families." (1996).

5. National Institute of Neurological Disorders and Stroke. "Huntington's Disease-
Hope Through Research." July 31, 2001.
www.ninds.nih.gov/health_and_medical/pubs/huntington_disease-htr.htm.