



Huntington's Disease
Society of America

GENETIC TESTING PROTOCOL FOR HUNTINGTON'S DISEASE

You can obtain a copy of the "Genetic Testing Protocol for Huntington's Disease"
by emailing HDSA at hdsainfo@hdsa.org

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FOREWORD

Since the advent of genetic testing for Huntington's disease, the Huntington's Disease Society of America (HDSA) has played a key role in establishing guidelines for safe and effective testing. As recent advances in both basic and clinical research lead to the promise of new opportunities for treatment and care, HDSA has revisited these guidelines to ensure that they continue to reflect best practices for both diagnostic and predictive testing.

This document was written by HDSA with input from clinicians, laboratory professionals, and individuals at risk for HD to provide guidance for genetic testing for Huntington's disease (HD).

In 1983, Huntington's disease became the first disease to be mapped to a previously unknown genetic location on chromosome 4. Over the past 30 years, genetic testing for Huntington's disease has progressed from the identification of linked genetic markers to the development of direct genetic testing. Throughout that history, groups such as the Huntington's Disease Society of America, the International Huntington's Association, and the World Federation of Neurology have provided recommendations for testing to health professionals wishing to provide such testing, as well as to individuals affected and at risk for HD who wish to pursue testing.

While technological advances have made genetic testing for HD faster, cheaper, and more accurate, predictive testing for HD remains a process with the potential to have profound implications for the life of an individual who chooses to be tested. So while we favor eliminating barriers to testing to the extent possible and maintaining flexibility in the way that testing is offered, experience has shown that the following elements are essential to the testing process: pretest counseling, informed consent and in-person results. A child **should not** be tested unless the child is exhibiting symptoms that cannot be attributed to any other condition.

HDSA hopes that this publication will be useful to those working with people with Huntington's disease and their families, as well as the families themselves.

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PREFACE

This protocol has been produced by the Huntington's Disease Society of America to assist genetic counselors and other healthcare professionals involved in the genetic testing process for Huntington's disease and to protect the well-being of individuals who choose to be tested.

The protocol is a framework of recommended procedures for testing; they are not regulations. Each provider, center, or institution that offers genetic testing for HD and each testing situation is unique. Providers must ensure that testing is performed safely despite variations among patients, personnel, and geography. The Huntington's Disease Society of America is particularly concerned about genetic predictive testing -- testing in asymptomatic individuals. HDSA maintains a list of centers where predictive testing protocols appear to meet the best practices described within. For more information on this list, please contact HDSA at hdsainfo@hdsa.org.

HDSA first published "Guidelines for Predictive Testing for Huntington's Disease" in 1989. A revision entitled "Genetic Testing for Huntington's Disease" was published in 1994 and revised in 2003. The current document reflects over two decades of experience with genetic testing for HD and is based on a review of the previous HDSA guidelines, the experiences of many who have been tested or who offer the tests, and the growing body of knowledge about genetic testing for many other diseases.

SECTION 1 INTRODUCTION

Huntington's disease (HD) is a hereditary neurodegenerative disorder. The HD gene is present from the time of conception and is inherited in an autosomal dominant fashion, meaning that each child of an affected parent, regardless of gender, has a 50% chance of inheriting the disease-causing gene. The prevalence of HD is estimated at 1/10,000 individuals in the United States; thus, the population to whom genetic testing might be applied includes approximately 30,000 affected individuals and 200,000 at-risk individuals.

The typical onset of HD symptoms is between ages 30-50. However, onset of symptoms has been seen in children under 5 years of age or as old as 90 years. There is an inverse relationship between the size of the pathogenic variant (CAG repeat expansion) and the age of symptom onset, in general, larger gene expansions are associated with earlier onset ages, although other factors may also influence the age of onset. Occasionally, individuals with a lower CAG repeat expansion may live up to or beyond a normal lifespan without developing symptoms. However, except for these unusual cases, the presence of an HD gene with a CAG repeat expansion is always associated with the development of HD symptoms

The early symptoms of HD vary and may be subtle enough to go undetected. These symptoms may include behavioral changes such as depression and mood swings, minor twitching, fidgeting, clumsiness, changes in gait, and lapses in judgment and memory. Symptom progression is likewise extremely variable. As the disease progresses, involuntary movements, particularly chorea, may become more pronounced. Speech and swallowing difficulties often develop and cognitive ability deteriorates. In the later stages of the disease, the affected individual is usually bedridden and totally dependent on others for all of his or her needs. The duration of symptoms may range from 10 to 25 years or more. Death is typically due to complications such as malnutrition or aspiration pneumonia.

For more information on Huntington's disease, including resources for professionals and family members, please visit www.hdsa.org or contact the HDSA National Helpline at (800) 345-4372 or by e-mail at hdsainfo@hdsa.org.

HISTORICAL BACKGROUND; CAG REPEAT EXPANSION

In 1983, in one of the early triumphs of the molecular genetic era, researchers at Massachusetts General Hospital located the marker for the gene that causes Huntington's disease (Gusella et al, 1983). This discovery paved the way for the development of a presymptomatic test for HD using a technique called linkage analysis, which was first offered to individuals at risk for HD on a research basis in 1986.

Because this test relied on tracing the inheritance of genetic markers linked to the huntingtin gene rather than the gene itself, analysis of DNA samples from multiple affected and unaffected family members was necessary and the test was only 95% accurate. As more markers closer to the HD gene were identified, the test became more accurate. By the late 1980s, over 20 centers around the country offered the genetic linkage test as a clinical service.

Ten years after the first marker was found, the HD gene itself was finally identified (Huntington's Disease Collaborative Research Group, 1993). The gene is known as the IT-15 gene, which encodes the huntingtin protein. The abnormal HD gene contains an expanded and unstable DNA segment, which is composed of the trinucleotide cytosine-adenine-guanine (CAG) repeated a number of times in a row. The repeating CAG fragment is longer on the expanded gene than on the normal huntingtin gene and is unstable, sometimes changing in length when it is passed to offspring. Worldwide experience suggests the following interpretations for the results of HD genetic testing (Nance, Paulsen, Rosenblatt, Wheelock, 2011):

CAG REPEAT SIZE

26 and below

27-35

36-39

40 and above

INTERPRETATION

Normal

Normal, unstable (sometimes called the "intermediate range")

Abnormal; reduced penetrance, unstable (sometimes called the "indeterminate range.")

Abnormal/Huntington's disease

To clarify this table further, any number of CAG repeats that is less than or equal to 26 is considered normal. Within this range, the size of the CAG repeat segment also appears to be stable; i.e., does not appear as prone to expansion. CAG repeat lengths within the range of 27-35 are also normal and they are not associated with symptoms of HD. However, the CAG repeat length tends to be more unstable in this range and can increase, so that a parent with a repeat number in this range can have a child whose repeat number is in the HD range. If the number of CAG repeats is within the range of 36-39, whether or when HD symptoms will develop cannot be predicted with certainty. Within this range, some individuals have been found to have classic symptoms of HD, while others have lived to be very old without developing the symptoms of HD. The gene is unstable in this range and may expand, so that a child may have a number of CAG repeats that is clearly within the HD range. CAG repeat lengths of 40 or greater are virtually always associated with the development of the symptoms of HD at some time during a normal life span.

Large increases in CAG repeat length are more likely to occur when the HD gene is passed on to a child by an affected father (Hendricks et al., 2009). While CAG repeat length is a significant factor in determining the age of onset of HD symptoms, it is not the only factor. The CAG repeat length does not predict with any accuracy when a particular individual's symptom onset will be or the clinical course that the disease may take. Two individuals with similar CAG repeat lengths may have different ages of onset and different symptomology.

A DIRECT GENE TEST FOR HD

Since the development of the direct test for the HD gene by analysis of CAG repeat length, many centers have been established around the country to provide the genetic counseling and psychological support services that allow predictive testing to be performed in a timely, sensitive, and knowledgeable manner. Although HDSA maintains a list of centers that meet the standards set forth in this protocol, HDSA does not certify, promote, or advertise any predictive testing center, nor does it have any means to monitor or modify how testing is actually performed at the centers or associated costs.

There is still no cure for HD and no treatment proven to delay the onset or slow the progression of the disease. Certain medications and treatments are available that sometimes help alleviate specific symptoms associated with HD. The emotional and ethical issues that accompany the diagnosis of HD or the detection of the presence of the disease-causing gene in an asymptomatic individual remain significant, potentially devastating, and unbalanced by medical benefits or advances. The importance of genetic counseling and support of the individual undergoing testing remains undiminished.

CLINICAL USES OF THE GENE TEST

The gene test is useful in three clinical situations: for predictive testing in an asymptomatic individual known to be at risk for carrying the gene, for confirmation of a suspected diagnosis of HD, and for prenatal diagnosis and preimplantation genetic diagnosis (PGD). Each of these clinical situations will be reviewed separately, and certain special situations will be discussed at the end.

Special consideration should be given to the cost and accessibility of genetic testing, since the cost of testing is often a deterrent for individuals considering genetic testing. HDSA encourages clinics to consider ways to make the testing process as inexpensive and accessible for the individual as possible.

SECTION 2

PREDICTIVE TESTING

In this section, the term “Individual” refers to the person who seeks a predictive genetic test, to distinguish him or her from the “patient” who seeks medical attention because of symptoms. Below, after a discussion of general principles important for predictive testing, is a list of the specific recommended components of the testing process.

In the United States, predictive testing is requested by a relatively small proportion of people at risk for HD. The reasons commonly given by those undergoing predictive testing include future planning regarding marriage, reproduction, career, finances, or simply a need to relieve uncertainty. Because there are currently no direct medical benefits from predictive testing, it is incumbent upon the health professional to help the Individual who requests the test to balance the potential psychological or social risks of testing against the benefits he or she believes it may provide. These potential risks may include changes in the Individual’s perception of self, stresses in relationships with friends or family, discrimination in the workplace or community, difficulties obtaining/retaining insurance such as disability, life, and long term care insurance, and other concerns related to privacy and confidentiality. In many testing centers, a team of designated members, the HD predictive testing team, has been assembled to provide the range of services and counseling that are appropriate for an Individual considering predictive testing.

The decision to take a predictive test for HD must always be an informed, carefully considered, and freely-chosen personal decision. An Individual must not be pressured into testing by a spouse, another family member, a health care provider, an insurance company, or an employer.

Timing

Predictive testing should ideally take place in a supportive environment during a time period when the Individual is not otherwise stressed. Testing must not be accompanied by a sense of urgency or emergency and should be considered in a cautious manner. It is important to include enough time in the counseling process so that the Individual can fully consider the implications of the test and have a chance to reconsider his or her decision.

Confidentiality

Confidentiality is of utmost concern to Individuals undergoing predictive testing, for whom the untimely release of private genetic information could have serious adverse effects on personal and professional relationships, community standing due to prejudices, or self-esteem. Testing centers must ensure that all appropriate measures are taken to preserve the privacy of genetic testing information and results without compromising the person’s medical safety.

Test results must not be divulged to anyone other than the Individual without his or her written consent. If test results are used for research purposes, all identifiers must be removed unless the Individual specifically permits otherwise. Only in exceptional circumstances, such as

prolonged coma or death, may information about an Individual's gene test result be released to the next of kin.

Any communication between the testing team and family members must be discussed in advance with the Individual. For example, if a blood sample from another family member is needed to confirm a genetic diagnosis of HD, the Individual should speak with the relevant family member first. The testing team must ask for guidance from the Individual about communications from the team, such as leaving voice mail messages, mailing HD materials to the home or workplace, or emailing.

Support System

The Individual is encouraged to identify a companion (such as a spouse or close friend) to accompany him or her through the testing process. The companion, by being physically present during counseling sessions, can gain insight into the Individual's testing experience and thus become a uniquely valuable source of support. The Individual is discouraged from bringing another at-risk person or someone who may have a negative or difficult reaction to the Individual receiving a positive diagnosis of Huntington's disease. An Individual who cannot or does not want to identify a testing companion cannot be excluded from testing.

Identification of a local counselor is also recommended, particularly if the Individual lives some distance from the testing site. The counselor may be a psychologist, social worker, school counselor, minister, or other professional. The counselor should be available for emotional support or counseling as needed. The predictive testing team must have permission from the Individual to communicate with the local counselor as needed to provide information about HD and predictive testing.

Active psychiatric problems must be stabilized before an Individual undergoes predictive testing. Predictive testing cannot proceed if the responsible health professional believes it would be harmful to the Individual.

Neurological Evaluation

Neurological evaluation may be offered prior to the predictive test to any Individual who is or might be concerned about possible symptoms. A normal neurological exam can sometimes be sufficiently reassuring that predictive testing is no longer desired. However, refusal of a neurological examination cannot exclude the Individual from predictive testing.

Recommended Components of Predictive Testing

The recommended components of predictive testing are shown in Table 1 and described starting on page 11. Many predictive testing centers have been established around the country where teams of experienced clinicians provide these services. Physicians are strongly advised to refer appropriate Individuals for testing to a designated HD predictive testing center.

Items listed in Table 1 are part of the recommended predictive testing process, but the order in which they occur is not rigid and may be varied as appropriate for a particular testing Individual or center.

HDSA recommends two in-person visits for an Individual requesting predictive genetic testing unless concerns on the part of the testing team arise during the initial call or first in-person appointment that would necessitate additional services.

Additional services beyond those listed may include (but not be limited to) neuropsychological testing, personality inventory, additional visits with the genetic counselor or mental health professional, establishment of contact with a counselor outside of the testing program, and scheduled post-test follow-up sessions. Additional support or counseling for the Individual's primary support person or family may sometimes be necessary.

Table 1.

<p>Recommended Components of HD Predictive Testing Process:</p> <ol style="list-style-type: none">1. Telephone Contact2. Visit 1<ul style="list-style-type: none">- Genetic Counseling- Sign Informed Consent Document- Mental Health Assessment- Neurological Exam- Draw Blood3. Visit 2<ul style="list-style-type: none">- Disclosure of Results in Person- Arrange Post-result Follow-up4. Follow-Up<ul style="list-style-type: none">- Prearranged phone call or in-person visit

1. Telephone Contact

The purpose of this call is to help the Individual at risk understand the genetic testing process. During the initial telephone contact, which must be by the Individual, information about the testing process, costs, and risks is provided by a healthcare professional experienced in genetic counseling and testing for HD. Concerns about symptoms and whether the Individual may wish to include a neurological exam as part of the predictive testing process are also discussed.

Insurance: An Individual will be advised to consider whether he or she wishes to obtain life insurance, disability insurance, and/or long term care insurance prior to testing, since these types of insurance are not protected by federal law. The healthcare professional will also discuss whether the Individual wishes to utilize his or her health insurance to pay for testing or pay out of pocket for these costs.

Other information gathered: Demographic and medical history information about the Individual is obtained. Pre-test tasks such as identifying a local counselor, confirming the diagnosis of HD in a family member, evaluating neurological or psychiatric symptoms, or obtaining any of the insurances described above are discussed and scheduled or performed if necessary. If the Individual requires more time to prepare for the testing process, telephone conversations may extend past one session.

Next steps: Subsequent to the call, the testing center sends a fact sheet or similar document to the Individual that outlines the testing process at its facility including costs (See sample information sheet provided by HDSA Center of Excellence at University of California, Davis Medical Center <https://www.ucdmc.ucdavis.edu/huntingtons/genetics.html>).

2. Components of Visit 1:

After the in-depth telephone conversation, the Individual comes in for the first visit to meet with the genetic counselor and receive a mental health assessment and a neurological examination if the Individual agrees to one, and, if the clinic feels comfortable about the Individual's safety, a blood draw is performed.

- **Genetic Counseling -- in person**
This includes a review of the family history, confirmation of the family diagnosis, and explanation of the Individual's risk status. The genetic counselor will review genetic principles that relate to HD and the gene test, including the risks, benefits, and limitations of the test (such as the possibility of results in the intermediate range and the inability to predict the age of onset based on repeat number alone). The genetic counselor will also explore the Individual's experience with HD and perceptions of the disease and discuss the potential burden of the test results, positive or negative, on the Individual and the family.
- **Documentation of informed consent**
A signed document signifies that the Individual freely consents to this procedure. A copy of the consent document may be sent with the blood sample to the testing laboratory to ensure that only Individuals who have received counseling are tested.
- **The Neurological Exam:** An exam may be part of the predictive testing process at certain testing centers but an Individual has the right to decline the exam if he or she so desires.
- **Mental Health Assessment**
The mental health professional assesses the Individual's current emotional state so that ongoing psychological problems, significant life stressors, or need for emotional support beyond what is available as part of the testing program can be identified and managed appropriately. It is important that the Individual not view a pretest mental health assessment as an obstacle to testing. Rather, he or she should understand that such tests might help counselors to identify those who may need greater emotional support during and after testing. The mental health professional reviews the Individual's support system so that a plan for accessing help within the home or community is clear before results are given. Specific ways to access emergency psychiatric services are provided. If the Individual is already seeing a mental health professional, some clinics will coordinate with that professional. The mental health assessment should be performed by a mental health professional who has training in suicide assessment, such as a social worker, nurse, physician, psychologist, or psychiatrist.

Adverse emotional responses constitute the major medical complication of predictive testing. In some instances, such as overt risk for suicide and/or major depressive symptoms, it is important for the mental health professional to initiate psychiatric treatment and stabilize the Individual before making the decision on whether to proceed with the test.

- **Review of the Potential Impact of the Test**

Many Individuals enter the predictive testing process after much thought about whether to be tested. It is incumbent on the testing center to review the potential impact of the test results with the Individual, both positive and negative, and to discuss the risks and possible broader impact of the test. The genetic counsellor must discuss not only the emotional impact of a “positive” result, but also implications of a “negative” result. Survivor’s guilt and feelings of “having to make up for affected members of the family” should be part of the comprehensive discussion of testing.

For some people, knowing whether they have HD can be very helpful for family planning decisions. Financial planning concerns are another reason people may benefit from testing. If an Individual is concerned that he or she is beginning to show symptoms of HD, he or she may find relief in learning whether HD is present. While the exact effects of the gene test cannot be known in advance, an informed decision to be tested requires that the Individual be aware of and prepared to face these uncertain and potentially negative consequences. Possible negative consequences include loss of self-esteem, as well as intense or painful emotional responses. The test can change the Individual’s relationships with siblings, parents, and his or her own spouse or children, sometimes in an unpredictable or negative fashion. Relationships with friends and acquaintances may be altered. Finally, the test results can also have deleterious effects on the Individual’s employability and insurability. Some centers also make provisions for counseling the applicant’s companion or other family members whose lives are affected by the results of the test.

3. Components of Visit 2:

- **Disclosure of Results in Person**

The genetic counsellor gives the results to the Individual in person to avoid any possible miscommunication about this life-altering information. A supportive friend or family member who is not at risk should accompany the Individual to the results visit. In-person communication also begins the process of post-test supportive counseling and allows specific arrangements for follow-up as needed. The Individual has the right to postpone or cancel result disclosure.

- A subsequent phone call or an in-person visit should be arranged prior to the end of the disclosure visit and should be based upon the Individual’s need for additional support.

4. Follow-up after Testing

Follow-up should be individualized to respond to the needs of the Individual. Ideally, the testing center should initiate contact within a few weeks of test results to assess the Individual’s adjustment to his or her results. Gene positive individuals should be provided with information about clinical trials that are available. A baseline neurological examination should be encouraged for gene-positive individuals who have not already undergone one, and additional visits for supportive counseling should be offered as needed.

SECTION 3

CONFIRMATORY AND DIAGNOSTIC TESTING

Confirmation of clinical diagnosis

Confirmatory testing by analysis of the HD gene is offered at or after the time of the clinical diagnosis of HD. The presence of a CAG repeat expansion in a person with HD symptoms confirms the clinical impression and supports a diagnosis of HD. The absence of a CAG repeat expansion in a person felt clinically to have HD must prompt a re-evaluation of the person's diagnosis and a reconsideration of the accuracy of the diagnosis in the family. Molecular confirmation of the diagnosis of HD in another affected family member might be indicated. However, it is not essential for diagnostic reasons to perform a gene test in all people with characteristic clinical features of HD and a molecularly confirmed diagnosis of HD in the family.

A person who comes in for predictive testing, but who shows symptoms that the clinician suspects may be Huntington's disease even though the person seeking testing does not notice, should be treated as undergoing predictive testing since, for that person, it is a predictive test.

A positive HD gene test does not determine whether an individual's symptoms are caused by the gene. Only a clinical examination can determine whether a clinical diagnosis of HD is warranted. The use of the HD gene test in a person whose symptoms are not typical of HD (such as pain, fatigue, unilateral neurological signs, isolated depression, or non-neurological symptoms) is strongly discouraged. A positive gene test could lead the physician or person to a false supposition that the symptoms are due to HD and thereby prevent appropriate diagnostic evaluation or treatment.

For some individuals and families, the confirmation of a clinical diagnosis of HD by a gene test is a devastating event, since it establishes a diagnosis that was previously just a suspicion; for others, it simply reiterates a recognized or expected diagnosis and adds no further psychological burden. Counseling prior to the gene test and the availability of psychological support after the test are important components of the diagnostic process. Those who are confirmed to be gene positive should be referred to available HD clinical trials.

Some people may get a test result in the "intermediate" zone. This can lead to some confusion for the Individual, since he or she will not be sure whether symptoms of Huntington's disease will ever develop or what risk his or her child might face. It is important for the counsellor to discuss with these Individuals what it means to have a gene test within these boundaries.

Absent Family History

The family history of HD may be absent because of adoption, early death of a gene-carrying parent, misdiagnosis of a family member, non-paternity, or a pathogenic variant from a parent in the high normal allele range. The probability of a person in the high normal allele range having an offspring with an expanded allele that may cause HD ranges from 1:6,241 to 1:951 (Hendricks et al., 2009). The diagnosis of HD may be unexpected in these cases, and provision should be made for post-test support and counseling for family members who may request it, as well as for the tested Individual.

Atypical Symptoms

Occasionally, an Individual may be strongly suspected of having HD despite atypical symptoms. This might apply to Individuals with prominent psychiatric symptoms, atypical dementia disorders, and unusual movement disorders, and to any child suspected of having HD. Physicians must carefully consider the value and potential implications of establishing the presence of the HD gene, recalling that the presence of the HD gene may not explain the Individual's symptoms. It may be appropriate in some circumstances to evaluate an Individual with atypical symptoms several times over the course of a year to monitor whether the condition is static, improving, or progressing in a manner consistent with HD, prior to obtaining a gene test. This is particularly important for children, in whom the presence of symptomatic HD is rare and different from adult symptoms, and for whom the premature detection of the HD gene may have a greater negative psychological and social impact.

SECTION 4 PRENATAL TESTING

Individuals or couples considering prenatal testing are advised to seek genetic counseling prior to a pregnancy. Many reproductive options are available to Individuals affected by or at risk for HD, of which prenatal testing is one. Samples for prenatal analysis of the HD gene may be obtained in two ways: by chorionic villus sampling at 10-12 weeks of pregnancy, or by amniocentesis at 14-20 weeks. Some couples may also desire preimplantation testing of a fertilized embryo. This requires the use of fertility drugs and other procedures available only at specialized *in vitro* fertilization centers.

Direct Gene Testing

Chorionic Villus Sampling (CVS) is offered at some clinics for women from their 10th through 12th weeks of pregnancy. Amniocentesis can be done from the 14th through 20th weeks of pregnancy. This process includes genetic counseling to explore the parents' questions and concerns and to educate them about the risks involved. It is important for parents to explore what they hope to gain from this procedure, especially if they are not planning to terminate the pregnancy. As with testing of asymptomatic minors, CVS and Amniocentesis take away the child's option not to know his or her gene status.

CVS and Amniocentesis can be done if a parent is at risk or if he or she has tested positive for the gene that causes HD. If a parent has decided not to test, then genetic counseling must include the impact for both the parents and child of getting a positive result for the fetus. Testing the fetus when a parent does not want to know his/her own gene status can lead to a difficult situation wherein the at-risk parent will come to know his or her genetic status as a result of the fetal test. These instances require careful consideration.

Preimplantation testing

The development of the technology to perform Pre-implantation Genetic Diagnosis (PGD) offers an option for couples seeking to have children who will be gene-negative and avoids issues associated with terminating a pregnancy. PGD begins with the couple undergoing *in vitro* fertilization (IVF). In IVF, eggs are collected from the mother by a transvaginal biopsy of the ovaries and then fertilized *in vitro* (in a dish) by sperm collected from the father. The collection of the eggs has to be carefully timed to the mother's menstrual cycle and involves drug treatment to enhance the ovulation process and careful monitoring by a fertility clinic prior to the biopsy.

Because only a few eggs can be collected in the biopsy and are receptive to fertilization for a brief time, fertilization is performed by injecting the sperm into the egg, which greatly increases the likelihood of successful fertilization. The process is known as "intracytoplasmic sperm injection" or ICSI.

The PGD test is performed on a single cell that is collected by a needle biopsy from the eight-cell embryo (day 3 of development). The HD gene test is performed on the DNA from this single cell allowing for the detection of the HD repeat sizes for that embryo. Only those embryos testing gene-negative are implanted.

This procedure involves specific procedures and very specialized equipment for the various biopsies, fertilization, and genetic tests. Those who perform these procedures are extensively trained specialists, and therefore the procedure can be very expensive.

It is important for couples considering PGD to receive genetic counseling before beginning the PGD process. There are several common questions that arise with PGD that should be discussed with a genetic counselor.

Accuracy: The main concern for PGD is that the procedure involves the PCR amplification of DNA from a single-cell, and there is the possibility for HD gene allele drop-out to occur. This means that the HD gene allele from one of the two chromosomes does not amplify and the test result is not precise. (Bui & Harper, 2002). Consequently, blood samples are collected from both parents so that DNA can be studied simultaneously to ensure that both a maternal and a paternal allele is detected. When both parental alleles are detected, the test is very accurate and comparable to traditional HD testing from blood (>99% accuracy).

Success Rate: *In vitro* fertilization continues to have a fairly low rate of successful pregnancy, with only 20% to 30% of couples achieving pregnancy per IVF cycle. (Mastenbroek et al., 2007). According to the most recent report by the CDC (2009), the overall pregnancy rate for IVF was 29.4% of all cycles (higher or lower depending on the age of the woman). The percentage of cycles that resulted in live births was 22.4% on average (again depending upon age of woman). Thus the success rate, even among experienced programs, does not lead to the majority of couples achieving their goal of a live born child. There is a 25% risk of multiple births using this method.

Risk for Birth Defects: IVF itself is not associated with an increase in the frequency of birth defects. However, PGD utilizes intracytoplasmic sperm injection, which is associated with an increased risk for birth defects. An increase of about 1.5 times as many birth defects is seen with this procedure (Davies et al., 2012; Win J. et al., 2012).

Expense: Many insurance companies do not cover this cost for genetic testing even when they may cover costs for infertility treatment. Since most women do not become pregnant during the first IVF treatment, parents using this route may need to undergo multiple IVF cycles in their efforts to have a child.

Non-disclosing test: Some programs offer PGD for couples who do not wish to undergo HD presymptomatic testing (Stern et al., 2002). In this circumstance, parental gene status is not revealed to the parent during the testing. This can lead to important ethical questions, especially if it is discovered that the at-risk parent is gene negative (Erez et al, 2010).

SECTION 5 TESTING OF MINORS

Minors should not undergo genetic testing unless there is a medically compelling reason, such as a clinical diagnosis or a strong suspicion of HD. In these unusual circumstances, testing must be preceded by a complete neurological and neuropsychological evaluation. Parental anxiety about a child's risk does not constitute a medically compelling reason for genetic testing. A positive gene test does not mean that a child's symptoms are necessarily due to HD, and premature confirmation of the presence of the HD gene in a child may distract the family or physician from identifying other causes of the symptoms and lead to improper management.

Because of the vivid historical examples of the abuse of genetic information in nonconsenting individuals, the principle of autonomy as embodied in the process of informed consent is held with particular importance in genetics. The goal of the prohibition against testing minors is to preserve the autonomy of the child to decide whether to be tested when the age of majority (usually 18) is reached. Predictive testing of minors currently has no medical benefits and the possibility for psychosocial harm and lowered self-esteem is high. The potential for discrimination at the workplace, at school, or by insurance providers is also proportionally greater in a younger individual. However, minors should not be discouraged from seeking genetic counseling if they have questions about their at-risk status or future options.

The recommendation not to test minors includes situations in which prospective adoptive parents wish to have a child who is at risk tested for the HD gene prior to adoption. If a negative test, showing that the child does not carry a gene with an expanded CAG repeat influences the prospective parents to proceed with adoption, a positive test might, conversely, consign the child to permanent foster care.

Exceptions to the prohibition against testing children might be made in the case of “emancipated” minors, such as those who are married or pregnant. Another consideration might be an older child at risk who is aging out of foster care and has major life decisions to make. Requests for testing by adolescents at risk may be considered on a case by case basis, but the primary consideration should be that the child or adolescent is making the request by and for himself or herself and not at the request of a third party, regardless of whether it is parents, foster parents, school employees, employers, physicians, or members of the justice system such as lawyers or judges.

ANONYMOUS TESTING

The advent of direct gene testing makes it possible for a person to be tested without the involvement or knowledge of other family members. All testing centers adhere to basic standards of medical confidentiality. However, some individuals have exceptional concerns about confidentiality and desire “anonymous” testing. Although anonymous kits or procedures are available for HIV testing and pregnancy testing, this approach has not yet been applied to genetic tests. Because there is no standardized definition of anonymity nor an accepted means to remove some or all identifiers from an Individual’s medical file or test requisition form, the center and the Individual must discuss and agree on how best to meet the Individual’s needs or desires. An Individual’s desire for anonymity may create a barrier to the supportive relationship that the counselor seeks to establish and can make subsequent care for psychological or neurological symptoms more difficult to provide. Some centers may decline to or may be unable to perform predictive testing anonymously, but depending on the situation or Individual seeking anonymous testing, other centers may be willing to work with the Individual to provide the desired service. Whether a person tests negative or positive for HD through an anonymous test, he or she may need to be retested at a later date for their medical file.

TESTING TWO PEOPLE WITH ONE TEST

Occasionally, an Individual may request predictive testing because his or her parent has a 50% risk of having HD, though the parent is not yet affected, is unwilling to be tested, or is alienated from the Individual. Performing this test is equivalent to testing two people, perhaps without the knowledge of, or even against the will of, one of the two parties. This is a challenging genetic counseling session in which *shared decision making* is crucial in determining whether the applicant’s desire to know his or her gene status supersedes the parent’s right not to know. A more in-depth discussion with the Individual is warranted in these cases to ensure he or she understands what his or her gene positive result means for the parent and siblings. If the whereabouts of the at-risk parent is known, every attempt should be made by the Individual to discuss his or her desire to be tested with the at-risk parent. Some parents may be aware of the Individual’s desire and agreeable to the decision to be tested, while others may not. Some centers may refuse the request because of the potential harm to the non-consenting parent. Other centers may consider such requests individually. Consultation with an institutional Ethics Committee or legal counsel may be helpful to a center that is considering such a request.

The second situation in which it is possible to test two people at once is when the Individual is an identical twin. If the twins truly are identical and not fraternal, testing one twin will reveal information about the other twin. This, too, is an ethically difficult situation, and counselors should explore, to the extent possible, the needs and desires of the other twin about testing as well as social circumstances and family relationships. Consultation with an Ethics Committee or legal counsel may be helpful.

RESULTS OF INTERMEDIATE ALLELES

Sometimes the person being tested receives a result in the intermediate or reduced penetrance range (27-39). People with this genetic determination might or might not eventually exhibit symptoms associated with HD. In this situation, a genetic counselor can help a person understand what this means for both the person at risk and his or her offspring. A discussion of this possibility should be mentioned during the initial genetic counseling session (Semaka et al., 2011; Brocklebank et al., 2009).

SECTION 6 CONCLUSIONS

Genetic testing for HD is a straightforward procedure, but should not be considered a simple blood test. An Individual who has a gene test should have access to an accurate and up-to-date interpretation of the results and competent support for the complex psychological and social consequences of the results. Although the medical value of predictive testing will change dramatically if treatments to prevent or delay the disease are developed, the psychological and social aspects will continue to be challenging, and the need for sensitive, timely, and accurate counseling will remain.

SECTION 7 REFERENCES

Brocklebank D, Gayan J, Andresen JM, Roberts SA, Young AB, Snodgrass SR, Penney JB, Ramos-Arroyo MA, Cha JJ, Rosas HD, Hersch SM, Feigin A, Cherny SS, Wexler NS, Housman DE, Cardon LR, International-Venezuela Collaborative Research Group. Repeat instability in the 27–39 CAG range of the HD gene in the Venezuelan kindreds: counseling implications. *Am J of Med Genet B: Neuropsychiatr Genet* 2009 Apr 5; 150B (3), 425-9.

Bui TH, Harper JC, (2002) Pre-Implantation genetic diagnosis, *Clinical Obstetrics and Gynaecology*, 16(5): 659-70

CDC (2009) Assistive Reproductive Technology Success Rate, WebMD, January 18, 2015

Davies MJ, Moore VM, Willson KJ, Van Essen P, Priest K, Scott H, Haan EA, & Chan A. Reproductive technologies and the risk of birth defects. *N Engl J Medicine*, 2012, May 10; 366(19), 1803-13.

Erez A, Plunkett K, Sutton VR, & McGuire AL (2010). The right to ignore genetic status of late onset genetic disease in the genomic era; Prenatal testing for Huntington disease as a paradigm. *American Journal of Medical Genetics Part A*, 152(7), 1774-1780.

Gusella JF, Wexler NS, Conneally PM, Naylor SL, Anderson MA, Tanzi RE et al (1983) A polymorphic DNA marker genetically linked to Huntington's disease. *Nature* 306: 234-238

Hendricks E, Latourelle J, Lunetta K, Lupple A, Wheeler V, MacDonald M, Gusella J, Myers R (2009) Estimating the probability of de novo HD cases from transmissions of expanded penetrant CAG alleles in the Huntington disease gene from male carriers of high normal alleles (27–35 CAG) *AJMG* 149

The Huntington's Disease Research Collaborative Group (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes, *Cell* 72: 971-983

Mastenbroek S, Twisk M, van Echten-Arends J, Sikkema-Raddatz B, Korevaar JC, Verhoeve HR, & Buys CH (2007). In vitro fertilization with preimplantation genetic screening. *New England Journal of Medicine*, 357(1), 9-17.

Nance M, Paulsen J, Rosenblatt A, Wheelock V (2011) *A Physician's Guide to the Management of Huntington's Disease (Third Edition)*, Huntington's Disease Society of America

Pickering SJ, Braude PR, Patel M, Burns CJ, Trussler J, Bolton V, & Minger S (2003). Preimplantation genetic diagnosis as a novel source of embryos for stem cell research. *Reproductive biomedicine online*, 7(3), 353-364.

Semaka A, Balneaves LG & Hayden MR (2013). "Grasping the Grey": Patient Understanding and Interpretation of an Intermediate Allele Predictive Test Result for Huntington Disease. *Journal of genetic counseling*, 22(2), 200-217.

Stern HJ, Harton GL, Sisson ME, Jones SL, Fallon LA, Thorsell LP, Getlinger ME, Black SH, & Schulman JD. Non-disclosing preimplantation genetic diagnosis for Huntington disease. *Prenat Diagn*, 2002 Jun 22(6): 503-7.

Sample information sheet provided by HDSA Center of Excellence at University of California, Davis Medical Center <https://www.ucdmc.ucdavis.edu/huntingtons/genetics.html>

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The Huntington’s Disease Society of America is the premier nonprofit organization dedicated to improving the lives of everyone affected by HD. From community services and education to advocacy and research, HDSA is the world’s leader in providing *help for today, hope for tomorrow* for people with HD and their families.

To learn more about Huntington’s disease and the work of the Huntington’s Disease Society of America, visit www.hdsa.org or call (800) 345-HDSA.