

GENETIC TESTING for HUNTINGTON'S DISEASE:

ITS RELEVANCE AND IMPLICATIONS

(Revised)

**United States
Huntington's Disease
Genetic Testing Group**



Huntington's Disease Society of America



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Genetic Testing for Huntington's Disease Revised HDSA Guidelines

February 2003

United States Huntington's Disease Genetic Testing Group

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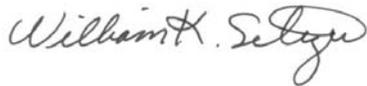
FOREWARD

Recent advances in both basic and clinical research have led to exciting new developments in our understanding of Huntington's Disease (HD) and have significantly affected the outlook and lives of those who live at risk or who suffer from this disease and their families. This publication was written to provide information about the diagnostic application of molecular genetic testing for HD, as well as to share the perspectives of clinicians, laboratory professionals and individuals at risk of HD about presymptomatic genetic testing for this disease.

First described in 1872 by Dr. George Huntington, HD is an autosomal disorder that affects most ethnic and racial groups. The clinical usefulness of testing for HD has paralleled advances in research that has led to the first clinical and observational trials for possible treatments. Identification of the HD locus to the short arm of chromosome 4 and linkage to an anonymous DNA marker in 1983 occurred through the analysis of a large Venezuelan population isolate. As DNA markers closer to the disease locus were identified, the first clinical application of this information became possible in 1986 with the advent of linkage analysis predictive testing for HD. For the first time, healthy individuals could be tested to determine their risk of developing HD before symptoms occurred. Linkage analysis requires testing of both affected and unaffected family members and is a lengthy, costly process. Ethical issues, including informed consent and the consequences of providing this information to healthy adults, prompted the development of practice guidelines by the World Federation of Neurology and the International Huntington Association in 1990.

In 1993, the HD gene was cloned and the mutation was identified as an unusual expansion of a CAG trinucleotide repeat sequence coding for a polyglutamine track within exon one. Thus, HD is grouped with other neurogenetic diseases that share a common mutational basis of abnormal trinucleotide expansions. This information has had a direct effect on diagnostic testing for HD and has made available confirmatory testing, diagnostic testing, and presymptomatic and prenatal testing.

Genetic Testing for Huntington's Disease - Its Relevance and Implications (revised) presents the current diagnostic usefulness of genetic testing for HD and discusses the results of surveys that evaluate issues related to testing individuals at-risk for this disease. This publication will be extremely useful to those working in the HD community and to all professionals - now and in the future - who care for patients with adult-onset genetic disorders.

A handwritten signature in cursive script that reads "William K. Seltzer". The signature is written in black ink and is positioned above the printed name.

William K. Seltzer, Ph.D., F.A.C.M.G.

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PREFACE

These guidelines have been produced by the Huntington's Disease Society of America, in conjunction with the United States Huntington's Disease Genetic Testing Group, to assist healthcare providers in administering the genetic test for Huntington's Disease, and to protect the well-being of those who choose to be tested.

The guidelines should be viewed as a framework of recommended procedures for testing; they are not regulations. Each provider, center, or institution that provides genetic testing for HD, and each testing situation, is unique, and 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 in asymptomatic individuals. HDSA maintains a list of centers whose predictive testing protocols appear to meet the guidelines described within.

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. The current document reflects over a decade of experience with genetic testing for HD, and is based on a review of the previous HDSA guidelines, the experience of many who have been tested and who provide the tests, and the growing experience with genetic testing for many other diseases.

1. INTRODUCTION

Huntington's Disease (HD) is a hereditary degenerative disorder of the central nervous system. It 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, with approximately 5 at-risk individuals for every currently affected person. Thus, the population to whom genetic testing might be applied includes approximately 25,000-30,000 affected individuals and 125,000-150,000 at-risk individuals.

The typical onset of HD symptoms is between ages 30-50. However, onset of symptoms has been seen in persons as young as 5 years or as old as 90 years. There is an inverse relationship between the size of the gene mutation (CAG repeat expansion) and the age of symptom onset, so that larger gene expansions are associated with earlier onset ages. Occasionally, individuals with a small 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 and with the 50% risk to each offspring.

The early symptoms of HD vary and may be subtle enough to go undetected. These symptoms may include minor twitching, fidgeting, clumsiness, changes in gait, lapses in judgment and memory, and in some individuals, behavioral changes including depression and mood swings. Symptom progression is likewise extremely variable. As the disease progresses, involuntary movements (chorea) 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.

2. HISTORICAL BACKGROUND; CAG REPEAT EXPANSION

In 1983, in one of the early triumphs of the molecular genetic era, researchers at Massachusetts General Hospital mapped the Huntington's Disease gene to a location on the short arm of chromosome 4 (Gusella et al, *Nature* 1983; 306:234-238). 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 markers linked to the HD 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 it was first mapped to chromosome 4, the HD gene itself was finally identified (Huntington's Disease Collaborative Research Group, *Cell* 1993; 72: 971-983). The gene is known as the IT-15 gene, which encodes the huntingtin protein. The gene is expressed in the brain, but the normal function of the huntingtin protein in the brain remains unknown. The abnormal HD gene contains an expanded and unstable DNA segment, which is composed of the trinucleotide, CAG, repeated a number of times in a row. The repeating CAG fragment is longer on the HD chromosome than on the normal chromosome and is unstable, often changing in length when it is passed to offspring. This trinucleotide, CAG, codes for the amino acid glutamine. The CAG expansion, therefore, causes the HD protein to contain more glutamine than it normally has. Worldwide experience suggests the following interpretations for the results of HD genetic testing:

CAG REPEAT SIZE**INTERPRETATION**

26 and below

Normal

27-35

Normal but potentially unstable

36-39

Abnormal with variable penetrance; unstable

40 and above

Huntington Disease

To clarify this 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 prone to expansion. CAG repeat lengths within the range of 27-35 are also normal, in that they are not associated with symptoms of HD. However, the CAG repeat length can be 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, it cannot be predicted with certainty whether or when HD symptoms will develop. Within this range, some people 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.

It is known that large increases in CAG repeat length are more likely to occur when the HD gene is passed on by an affected father. 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.

3. A DIRECT GENE TEST FOR HD

Since the development of the direct test for the HD gene by analysis of CAG repeat length, over 80 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 which meet the standards set forth in the 1994 guidelines, 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.

Although the direct gene test allows an individual to be tested without the need for blood samples from multiple family members, it is still important for the clinician to confirm the accuracy of the HD diagnosis in the family. Thus, it is sometimes necessary to obtain a blood sample for analysis of the HD gene from an affected family member prior to performing a predictive or prenatal test.

As the new century begins, there is still no cure for HD, and no treatment proven to delay the onset or slow the progression of the disease. Therefore, 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 counseling and support of the individual undergoing testing remains undiminished.

4. CLINICAL USES OF THE GENE TEST

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

A. CONFIRMATORY AND DIAGNOSTIC TESTING

Analysis of the CAG repeat sequence in the huntingtin gene may be of use in three diagnostic situations.

1. Confirmation of clinical diagnosis

Confirmatory testing by analysis of the HD gene may be 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 patient'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 to perform a gene test in all patients with characteristic clinical features of HD and a molecularly confirmed diagnosis of HD in the family.

The HD gene is present from the time of conception. Therefore, 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 patient 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 patient to a false supposition that the symptoms are due to HD and thereby prevent appropriate diagnostic evaluation or treatment.

For some patients and families, the confirmation of a clinical diagnosis of HD by a gene test is a devastating event, as 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.

2. Absent family history

The family history of HD may be absent because of adoption, early death of a gene-carrying parent, nonpaternity, or because there truly are no affected family members in previous generations. New mutations probably account for 5% or less of HD-affected individuals in these families. Because of the implications of an accurate diagnosis to other family members and because of the prognostic implications for the affected person, gene testing is critical to confirm the clinical diagnosis of HD. 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.

3. Atypical symptoms

An occasional patient may be strongly suspected of having HD despite atypical symptoms. This might apply to individuals with prominent psychiatric symptoms, atypical dementing disorders, unusual movement disorders, and any child suspected of having HD. Physicians should 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 patient's symptoms. It may be appropriate in some circumstances to evaluate a patient 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 for whom the premature detection of the HD gene may have a negative psychological and social impact.

B. PREDICTIVE TESTING

In the United States, predictive testing is requested by a 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 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 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 or keeping insurance, unfavorable adjustment of disability benefits, and other concerns related to privacy and confidentiality. In many centers, a team of designated individuals, 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 should always be an informed, carefully considered, and freely chosen personal decision. Individuals should not be coerced into testing by a spouse, another family member, a physician, an insurance company, or an employer.

In the discussion below, the term "applicant" refers to the individual who seeks a predictive genetic test, to distinguish such individuals from "patients" who seek medical attention because of symptoms. After discussing general principles important for predictive testing, we list specific recommended components of the testing process.

1. Offer neurological evaluation

Some predictive testing applicants are concerned about neurological symptoms at the time that they present for testing. These individuals, if found to have a normal neurological examination, may be reassured to the extent that they no longer desire predictive testing. While some applicants discuss their symptoms during the counseling process, others may be unwilling or unable to articulate their concerns or their own self-diagnosis. The HD gene test cannot determine whether a patient has HD symptoms or

not, but it has the potential to corroborate a patient's own self-diagnosis of HD, which can in turn lead to a lack of appropriate evaluation and treatment of the symptoms or to psychological distress. Only a neurological examination can determine whether the applicant in fact has signs of HD. Because of the possibility of unvoiced concerns about HD symptoms, many centers offer neurological examinations routinely to all applicants prior to predictive testing. Even where the neurological examination is not routine, it should be offered at any point in the testing process if concerns about symptoms arise. Refusal to undergo a neurological examination should not necessarily exclude an applicant from predictive testing.

2. Timing

Predictive testing should ideally take place during a time of otherwise low stress in a supportive environment. Testing should 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 applicant can fully consider the implications of the test and have a chance to reconsider his or her decision.

3. 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, stature in the community, or self-esteem. Testing centers should ensure that all appropriate measures are taken to preserve the privacy of genetic testing information and results, without compromising the patient's medical safety.

Test results should not be divulged to anyone other than the applicant without written consent of the applicant. If test results are used for research purposes, all identifiers should be removed unless the applicant 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 other than the applicant should be discussed in advance with the applicant; ideally, the applicant should speak with the family members in advance. For example, if a blood sample from another family member is needed to confirm a genetic diagnosis of HD, the applicant should speak with the relevant family member first. The testing team should ask for guidance from the applicant about communications from the team, such as leaving voice mail messages, mailing HD materials to the home or workplace, or emails.

4. A companion; a local counselor

An applicant should be 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 applicant's testing experience and thus become a uniquely valuable source of support. The applicant is discouraged from bringing another at-risk individual as a source of support. Individuals who cannot or do not want to identify a testing companion should not be excluded from testing.

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

5. The predictive testing process

The components of predictive testing are shown in Table 1 and described in detail on page 22. Over 80 predictive testing centers have been established around the country, where teams of experienced clinicians provide these services. Physicians are strongly advised to refer appropriate applicants for testing to a designated HD predictive testing center.

Items are listed in Table 1 in the order in which they might typically be performed; however, this order is not rigid, and may be varied as appropriate for a particular testing applicant or center. Additional services beyond those listed may be recommended for certain individuals including (but not limited to) neuropsychological testing, personality inventory, additional visits with the genetic counselor or psychologist, establishment of contact with a counselor outside of the testing program, and scheduled post-test follow-up sessions. Additional support or counseling for the applicant's primary support person or family may sometimes be necessary.

A predictive gene test should not be performed in lieu of neurological or psychiatric evaluation of an applicant who is manifesting symptoms of HD. Neurological evaluation should be offered to any applicant who is or might be concerned about possible symptoms prior to proceeding with the predictive test. Active psychiatric problems should be stabilized before an applicant undergoes predictive testing. Predictive testing should not proceed if the responsible health professional believes it would be harmful to the applicant.

Table 1.

<p style="text-align: center;">Components of HD predictive testing process:</p> <p style="text-align: center;">Initial telephone contact Offer neurological evaluation Genetic counseling Sign informed consent document Psychological assessment Review of the potential impact of the test Disclosure of results in person Arrange post-result follow-up</p>	<p><u>Initial telephone contact</u> During the initial telephone contact, basic information about the testing process and its costs and risks is given. Demographic and medical history information about the applicant is obtained.</p> <p><u>Neurological evaluation</u> Neurological evaluation should be offered to any applicant who is concerned about or suspicious of HD symptoms. As noted above, a normal neurological examination may relieve the applicant's concerns and obviate the need for genetic testing.</p>
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Genetic counseling

This includes a review of the family history, confirmation of the family diagnosis, and explanation of the applicant's risk status. Genetic principles that relate to HD and the gene test are reviewed, including the risks, benefits, and limitations of the test (such as the possibility of results in the intermediate range, or the inability to predict the age of onset based on repeat

number alone). Alternatives to genetic testing are discussed. Often the genetic counselor will explore the applicant's experience with HD and perceptions of the disease, and discuss the potential burden of the test results on the individual and the family. Pre-test tasks are discussed and scheduled or performed if necessary (such as identifying a local counselor, confirming the family diagnosis by testing an affected person, evaluating neurological or psychiatric symptoms, or obtaining insurance).

Documentation of informed consent

A signed document signifies that the applicant freely consents to this procedure with an understanding of the potential risks and benefits and knowledge of the alternatives. 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 and consent are tested.

Psychological assessment

The applicant's current emotional state is assessed, so that those with ongoing psychological problems, significant life stressors, or needs for emotional support beyond what is available as part of the testing program can be identified and managed appropriately. It is important that applicants not view pretest psychological assessment as an obstacle to testing. Rather, they should understand that such tests might help counselors to identify those who may need greater emotional support during and after testing. The applicant's support system is reviewed, 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.

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 to initiate psychiatric treatment and stabilize the individual before making the decision whether or not to proceed with the test.

Review of the potential impact of the test

Most applicants enter the predictive testing process with a strong view of the likely benefits of testing to themselves. It is incumbent on the testing center to balance this view of the benefits with a discussion of the risks and possible broader impact of the test. Possible dangers of testing include loss of self-esteem, as well as intense or painful emotional responses. The test can change profoundly the applicant'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 applicant's employability, insurability, or social standing in the community. While the exact effects of the gene test in any of these areas cannot be known in advance, an informed decision to be tested requires that the applicant be aware of and prepared to face these uncertain and potentially negative consequences. Some centers also make provisions for counseling of the applicant's companion or other family members whose lives are impacted by the results of the test.

Disclosure of results in person

Every effort should be made to give results to the applicant in person, to avoid any possible miscommunication about these life-altering results. In-person communication also begins the process of post-test supportive counseling and allows specific arrangements for follow-up as needed. The applicant has the right to postpone or cancel result disclosure.

Follow-up after testing

Follow-up should be individualized to respond to the needs of the applicant. Ideally, the testing center should initiate contact within a few weeks of test results, to assess the applicant's adjustment to his or her results. 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.

C. PRENATAL TESTING

INDIVIDUALS OR COUPLES CONSIDERING PRENATAL TESTING ARE ADVISED TO SEEK GENETIC COUNSELING PRIOR TO BECOMING PREGNANT. Many reproductive options are available to individuals affected with 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 biopsy at 10-11 weeks of pregnancy, or by amniocentesis at 14-18 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.

1. Direct gene testing

When one parent is known to carry the HD gene and wants to determine the gene status of the fetus, fetal cells can be obtained for genetic analysis by chorionic villus sampling (a biopsy of the placenta taken by an instrument inserted through the vagina and cervix), or by amniocentesis (a needle inserted through the abdomen into the uterus). Genetic counseling must precede any prenatal test, so that the options of pregnancy termination or bearing a child known to carry the HD gene can be discussed in advance, as well as the risks of the testing procedure itself.

Some at-risk women may seek prenatal testing when their own gene status is unknown, and spouses of at-risk men may request prenatal testing at a time when the at-risk spouse's gene status is unknown. In either situation, counseling must clarify that in addition to learning the fetal gene status, the prenatal test may also disclose the gene status of the at-risk parent. This is equivalent to testing two individuals, possibly without consent from or against the wishes of, one of the individuals. This is an ethically difficult situation for the genetic counselor, and only in unusual circumstances would such a test

be appropriate. Detailed counseling to explore the individual's reasons for seeking testing, and to discuss alternatives to prenatal testing must be undertaken prior to testing.

2. Prenatal exclusion testing

A prospective parent who is at 50% risk and who does not wish to know his or her own genetic status may request a non disclosing prenatal test, also known as prenatal exclusion testing. In this situation, the HD gene itself is not tested, but rather markers close to the gene, which can determine whether the fetus has received the at-risk parent's maternally or paternally derived chromosome 4. If the fetus has received the chromosome that the at-risk parent received from the affected grandparent, then the fetus has a 50% chance of having an abnormal HD gene. If the fetus received the chromosome that the parent inherited from the unaffected grandparent, then the possibility of HD in the fetus has been excluded. In neither case has the parent's risk status been changed from 50%.

This test requires the comparison of DNA markers from several family members, and must be planned prior to a pregnancy. DNA markers adjacent to the HD gene are not currently widely used in clinical service laboratories, so it may take time to identify a laboratory that is able to perform the desired analysis. Counseling should review the potential inaccuracies inherent in DNA marker analysis, and the possibility that the results will be noninformative, as well as any concerns the family may have about terminating a pregnancy because of a 50% risk of carrying the HD gene.

3. Preimplantation testing

Preimplantation testing refers to a procedure performed in specialized in vitro fertilization centers. A woman is given fertility drugs to induce production of several eggs at a time. The partner's sperm are joined with the eggs in vitro, and several embryos are obtained. At a very early stage in embryogenesis, a single cell is removed from each embryo for genetic analysis. Only an embryo free of the HD gene mutation is implanted into the uterus. Preimplantation testing does not require the at-risk individual to confront his or her own gene status, and it does not require consideration of pregnancy

termination. Preimplantation testing is performed only at a few specialized centers and requires extensive counseling, preparation, and expense.

5. SPECIAL SITUATIONS

A. 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 should 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 Nazi racial hygiene and ethnic cleansing efforts), the principle of informed consent is held with particular importance in genetics. Predictive testing of a minor violates this principle, as a minor is not legally able to give consent. Exceptions might be made in the case of "emancipated" minors, such as those who are married or pregnant. Predictive testing of minors has no medical benefits, and the potential for psychosocial harm and lowered self-esteem is high. The potential for discrimination at the workplace, school, or insurance agency is also proportionally greater in a younger individual.

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, might a positive test, conversely, consign the child to permanent foster care?

B. 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 applicants 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 not a standardized definition of anonymity or an accepted means to remove some or all identifiers from an applicant’s medical file or test requisition form, the center and the applicant have to discuss and agree on how best to meet the applicant’s needs or desires. An applicant’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 perform predictive testing anonymously, but depending on the situation or applicant, other centers may be willing to work with the applicant to provide the desired service.

C. TESTING AN INDIVIDUAL AT 25% RISK

Occasionally, an applicant may request predictive testing because his or her parent has a 50% risk of having HD but is not yet affected, is unwilling to be tested, alienated from the applicant, or deceased. This is equivalent to testing two individuals, perhaps without the knowledge of, or even against the will of, one of the two parties. This is an ethically difficult situation for the genetic counselor, who must decide whether the applicant’s desire to know his gene status supersedes the parent’s right not to know. Some centers may refuse the request, because of the potential harm to the nonconsenting 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.

6. CONCLUSIONS

Genetic testing for HD can be done safely, but it should not be considered a simple blood test. Individuals who have a gene test should have access to an accurate and up-to-date interpretation of the results, and 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.

