



Guideline

Title

Pre-symptomatic and Predictive Testing for Genetic Disorders

Document Number

2014GD02

Publication Date

March 2014

Replaces

Pre-symptomatic and Predictive Testing for Genetic Disorders 2005GD01

Review Date

2017

INTRODUCTION

Pre-symptomatic and predictive testing using DNA (or in some cases RNA, protein or other analytes) is now available for many disorders. Pre-symptomatic testing refers to a genetic test performed on a person who has a family history but no symptoms of a specific disorder at the time of testing, to determine whether or not the mutation for that disorder (known to be present in the family) has been inherited. If the test reveals that the mutation is present, the person is almost certain to develop the disorder at some time in the future, provided he or she lives long enough. Huntington disease, familial adenomatous polyposis (FAP) and myotonic dystrophy are examples of disorders to which the term 'pre-symptomatic' testing applies.

Predictive testing refers to a genetic test performed on a person who has a family history but no symptoms of a specific disorder at the time of testing, to determine whether or not the mutation for that disorder (known to be present in the family) has been inherited. If the test reveals that the mutation is present, the person has an increased predisposition to develop the disorder at some time in the future. Not everyone with this increased predisposition will develop the condition. Testing for mutations in BRCA1 and BRCA2 (breast cancer) and MLH1 and MSH2 (colon cancer) are examples of predictive testing.

Clinical geneticists and genetic counsellors, in common with many other health care professionals, are aware of the impact genetic testing can have on individuals and their families. Experience in offering this service to people, such as to those at risk of Huntington disease or cancer, is well established. However, with the growth of both knowledge and technology, there are progressively more situations where testing is possible and new groups of health professionals and potential test users need to become familiar with these tests and the context in which they are used. Clinicians need to consider the long term consequences when requesting testing, to determine whether testing is screening, diagnostic, pre-symptomatic or predictive. Practice guidelines have been developed to describe some of the issues and principles which apply in pre-symptomatic/predictive testing and are intended to guide all health professionals who undertake such testing.

The practice guidelines for this policy apply to pre-symptomatic/predictive testing of adults who are capable of making an informed choice and who are at risk of developing a known and serious genetic or multifactorial condition. They do not apply to community screening for genetic disorders (that is, screening people who do not have a significant family history and who are therefore not at increased risk). We assume that the test will have been validated and be capable of giving reasonably definite predictions in most cases.

It is very important to ensure close liaison between clinicians, counsellors and laboratories involved in providing the test to ensure that the current validity of any available tests is fully understood, and that inter-disciplinary discussion and audit are carried out regularly. Those using the practice guidelines should note that there may be relevant Commonwealth and State laws which will take priority.

GUIDELINES

How should the test be provided?

Testing and counselling are best provided by multi-disciplinary groups with experience in pre-symptomatic/predictive testing and awareness of the personal, family and social consequences of testing. Each group will have an appropriate mix of suitably qualified and skilled professionals e.g. genetic counsellors, clinical geneticists, social workers, other clinical specialists expert in the disorder, and laboratory scientists. All professionals involved must be knowledgeable about the genetic disorder for which the test is being performed, including the features of the laboratory test and any problems which could arise regarding accuracy or interpretation.

The testing team should have a program of quality control and audit similar to the standards recommended by the HGSA. Clinicians, counsellors and laboratories can all benefit from periodic formal and informal assessment of performance and clear objectives should be in place to facilitate such programs. Laboratories which perform predictive tests should develop protocols, in consultation with those delivering the clinical aspects of the testing program, governing the conditions under which samples will be accepted for testing.

Tests should only be offered in the context of accurate diagnosis of index cases and proper risk assessment for the person requesting testing. The diagnosis needs to be confirmed clinically in relevant affected family members and, where possible, at the molecular level in at least one affected family member. Ideally, the gene mutation responsible for the disorder in the family should be known. The limitations of testing without a known mutation should be discussed. It may be necessary to perform or repeat a diagnostic test before proceeding to predictive testing. In general, the person requesting testing will be the one to approach family members who need to be involved in the testing process (for a blood sample, clinical examination or access to medical/genetic records). This should be done with sensitivity, recognizing that some family members may not wish to have genetic testing or even to talk about the condition.

COUNSELLING ISSUES

Aim of Counselling

“Irrespective of the disease being tested for, it is suggested that the psychological aim of pre-symptomatic testing is to foster emotional insight and understanding that will help patients/clients in their decision-making process about testing and their subsequent adjustment to the result.”²

It should be ascertained at the outset why the individual has come forward for testing and his/her expectations of the test. Even if the person has made a firm decision to proceed with testing, it is essential that he or she is provided with information, counselling and support during the testing process and afterwards. Those providing predictive testing need to ensure that all the implications of testing have been considered, and counselling should be available for as many sessions as necessary. Patients/clients should be encouraged to bring a partner, family member or friend to counselling sessions, in particular, to the result session.

Information discussed during counselling should include:

Informed Consent

It is important that all tests are performed only on individuals who have made an informed voluntary decision to have the test, and there should be no pressure from third parties, including family, friends, health professionals, insurance companies or employers.

It is recommended that, prior to written consent being sought, written as well as oral information is given in clear and concise English. It may also be necessary for the material to be translated from English to another language. General information about the disorder being tested will include the clinical features, age of onset, variability of clinical features, the genetic basis and pattern of inheritance, and availability of treatment. Details of the test and the testing process will be explained. Reproductive options will be discussed, if relevant. Information should be provided about lay organizations and genetic registers that exist to inform and support families with a genetic disorder.

The clinician and/or counsellor should make every effort to ensure that the pre-test information is understood. The individual to be tested should have the opportunity to discuss testing with family, friends or significant others, if he or she wishes. A consent form must be read, understood and signed by each person tested. While the consent form would ideally be designed specifically for each individual test, this is impractical. Therefore the generic consent form attached provides a checklist of the main points to be addressed.

If someone is not able to give consent, due to mental or physical illness or disability, samples should only be taken if appropriate consent is given by the person's legal guardian, after discussion and counselling, and if it is essential to reach a diagnosis which will be of value to the individual or other family members. The rights of the ill or handicapped person should be considered as well as those of other family members.

Practical Information

- the purpose of the test
- how the test is done
- what tissue will be taken for testing (blood/mouthwash/skin biopsy)
- the accuracy of the test
- whether it is possible for the test to give an uncertain result i.e. not show with certainty whether the person tested has or has not inherited a disease-causing mutation
- what the result will mean for the tested individual if it shows that the mutation has been inherited or if it shows that the mutation has not been inherited
- what the result will mean for other family members (especially spouse, children, parents, brothers and sisters)
- what options there might be for future reproduction (e.g. prenatal diagnosis, preimplantation genetic diagnosis, donor gametes)
- explanation that a result showing that the mutation has been inherited may not give information about age of onset, the precise symptoms which might occur, or the severity of symptoms. For some disorders, even though it is demonstrated that the mutation has been inherited, it is possible that symptoms will never develop during the lifetime of the person tested
- the current state of knowledge about the predictive value of the test and the fact that this could change as further information is obtained (eg for multi-factorial conditions)
- that the test will not provide information on conditions apart from the one for which it tests
- that in some instances, the test might reveal non-paternity or non-maternity
- that there are alternatives to testing, such as not taking the test at all, or storing DNA for later use by oneself or the family, or regular clinical review
- the person requesting the test will determine who can have access to the test result and who can know that the test has been performed. However at the present time the blood or tissue tested remains the property of the testing laboratory and may be needed for substantiation or validation of the result at a future time. When retention of samples is at odds with cultural practice, the health professional should discuss the options of respectful retention, return or destruction of samples
- the testing laboratory will not use DNA samples for purposes other than those agreed to in the consent form. It will store the DNA in good faith but cannot guarantee its viability for future use

Confidentiality of Result

Those being tested must be reassured that their results, and the fact that they have undergone testing, will be confidential between themselves and the testing team, and will not be revealed to others without their specific agreement and written consent. However it should be emphasized that, although the test results are confidential, there is still a possibility they might be revealed, either under subpoena or by someone informed of the result by the person tested. Possible consequences e.g. for employment, insurance should be explored, if relevant.

Provision needs to be made for the release of results, if necessary, to family members or guardians after the death of the person tested or after loss of testamentary capacity.

The details of the mutation causing the disorder in the family can be made available to laboratories which have been asked to test other family members, or to genetic registers, where appropriate, providing that doing so does not reveal any individual's pre-symptomatic or predictive status.

Psychosocial and Ethical Implications

- that it is possible to withdraw from the testing process at any stage
- that the emotional impact of possible test results on oneself and other family members should be considered
- that counselling will be available after the test result has been given
- that a positive test result is likely to adversely affect the ability to obtain or upgrade insurance policies (such as life or income protection insurance). Once tested, applicants for insurance have a duty to disclose their genetic test result when applying for a new or upgraded insurance policy
- that having a pre-symptomatic/predictive test has the potential to change relationships within the family
- that the test result can change the risk of other family members who have not requested testing e.g. children. In certain circumstances (e.g. testing of persons at 25% risk for a dominant disorder) it may reveal that an asymptomatic parent must have the mutation and will develop the disease. Although this should not override a person's access to testing, it should be considered and discussed in counselling before testing. Efforts should be made to involve other at risk relative(s) in counselling, where possible. It is important to discuss whether, and how, other family members should be approached after test results are known. Another circumstance where further discussion should be undertaken is where an identical twin wishes to have testing.
- that pre-result physical and psychological assessment is recommended for those undergoing pre-symptomatic testing for some disorders e.g. Huntington disease

Length of testing process

People should not rush into a pre-symptomatic/predictive test. It is usually advisable to allow an appropriate period (e.g. some weeks), between providing information and counselling, and obtaining consent for a test and taking the sample. An exception to this is if the at-risk individual or their partner is pregnant and they would consider prenatal testing.

The person being tested should be given a clear idea of the timetable for the testing process once the counselling process is complete and the test sample taken. How the result information will be communicated (usually face-to-face) where and by whom should also be outlined.

The laboratory should carry out the test with minimum delay once the test sample has been received.

Giving Results

If at all possible, the results should be given personally by the person who provided counselling before the test (or one of the members of the team providing testing). It should be made clear that the same procedure will be followed regardless of the result. The participant should be encouraged to bring a support person/s (family and/or friends) to the result appointment. A support network (family, friends, minister of religion, community groups, health and welfare professionals) should have been identified beforehand. If appropriate, lay and professional support organizations can offer additional help to persons undergoing testing both prior to testing and in the post-test period.

Some individuals may ask that their result be given by someone outside the testing team e.g. the family doctor or another health professional, and this should be agreed to, if appropriate, provided that the usual post-test information, support, counselling and follow-up is provided by that health professional, or jointly with the team.

Prior to the result appointment the need for post-test counselling should be discussed with the participant, bearing in mind that post-test counselling may be as important for a negative as a positive result. The timetable for follow-up, agreed prior to testing, should be reviewed at the result session, and arrangements made for the first follow-up contact.

Special Situations

There are certain situations that require special consideration.

Children should, in general, only have pre-symptomatic/predictive testing when the resulting information will be used to help with their health management in the immediate future, and not simply because parents wish to know. However, the age at which pre-symptomatic/predictive testing can be offered to a child should be given consideration by the testing team (see HGSA policy on testing of children and adolescents) and may change over time with emerging technologies and advances in treatment.

When pathology material from someone who has died is used to establish diagnosis or family inheritance pattern, the material itself belongs to the laboratory and not the family, but the usual counselling and clinical sensitivities should be applied.

Special care should be taken if a pre-symptomatic or predictive test is requested by someone who appears to be affected by the disorder. This may reflect the psychological defense mechanisms of the individual (e.g. denial), which can be important for maintaining well-being and social functioning. A clinical opinion may be the next appropriate step after counselling/discussion, rather than testing. If appropriate, diagnostic testing can follow clinical assessment to confirm a clinical diagnosis. Alternatively, pre-symptomatic/predictive testing may proceed if the diagnosis is not confirmed, or if the person may react adversely to a diagnosis at that time.

GENERIC CONSENT FORM

Pre-symptomatic/predictive genetic testing for (disorder X)

1. Identifying details of test subject or parent/guardian
2. Statement of consent to the procedure(s) (venipuncture, collection of mouthwash cells) which will be used to obtain cells so that DNA or RNA can be extracted and used for the agreed purposes below
3. Statement of consent for use of the above DNA for one of more of the following purposes:
 - pre-symptomatic/predictive genetic testing for self
 - genetic testing by a gene tracking (linkage) method to assist with pre-symptomatic/predictive testing for other family members
 - research into (disorder X)
 - storage of DNA or cell lines for later use
 - other

4. Statement of limitations of, and possible unexpected outcomes of, the test including:

Mutation Detection

- the test can show that the disease-associated mutation has been inherited but not the age of onset or range/severity of the clinical features
- some tests may not give a definite answer e.g. triplet repeat results in the intermediate range (i.e. between the 'normal' and 'abnormal' ranges)
- the test may reverse the result of a test done previously by a gene tracking (linkage) method
- the test may reveal the status of the at-risk but as yet asymptomatic parent or identical twin.
- occasionally a test will be done when no mutation has yet been defined in an affected family member; in this situation, a negative test result ('no mutation detected') will provide very limited information

Linkage testing (Gene tracking)

- the test may not be informative for the test subject or some relatives, ie it will not be possible to track the mutant gene in the family with available markers
- the test will have specified error rate due to genetic recombination

With both mutation detection and linkage testing, the test may reveal non-paternity or non-maternity of a presumed natural parent

5. **Statement about confidentiality:**

The test result, and the fact that I have had a pre-symptomatic/predictive test, will not be given to any other person without my written consent, except in the following circumstances:

- after my death, to my next-of-kin
 - if I lose testamentary capacity, to my guardian
 - other circumstances(specified)
 - the result will be held by (name of testing centre) and will be known by those who participated in provision of the test
 - the details of the mutation causing the disorder in the family can be made available to laboratories which have been asked to test other family members, or to genetic registers, where appropriate, without revealing any individual's name and genetic status
6. Statement that the blood or tissue tested has been voluntarily given to the testing laboratory and that DNA remaining after the test is done, at the present time will be the property of the testing laboratory. It will be stored in good faith, but its integrity cannot be guaranteed
7. Statement along the following lines:
'(Name of health professional) has explained the test procedure and consequences of testing to me. I have had the opportunity to ask questions and understand the information provided. I understand that I may withdraw from the testing process at any time.'
8. Signature and name of test subject/guardian, date of consent, and signature and name of witness
9. Explanation of terms used in the consent form eg DNA (deoxyribonucleic acid: the chemical compound of which genes are made); mutation (changed information in a gene which may lead

to a disorder); cell lines (cells from blood or other tissues kept alive in the laboratory); gene tracking/linkage: the tracking through a family using 'markers' to identify the likelihood of the presence or absence of a mutation in family members).

References

1. NHMRC (2000). Ethical Aspects of Human Genetic Testing: An Information Paper. www.nhmrc.health.gov – publications/ethics/human.
2. Soldan J, Street E, Gray J, Binedell J, Harper PS (2000). Psychological Model for Presymptomatic Test Interviews: Lessons Learned from Huntington Disease. *J Genet Couns*, 9:15-31.