



Special Feature

Recommendations for the predictive genetic test in Huntington's disease

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**R MacLeod^{a,t,‡}, A Tibben^{b,t,‡},
M Frontali^{c,t},
G Evers-Kiebooms^{d,t},
A Jones^{e,‡},
A Martinez-Descales^{f,t,‡}, RA
Roos^{g,t,‡} and Editorial
Committee and Working Group
'Genetic Testing Counselling'
of the European Huntington
Disease Network^{t,‡}**

^aGenetic Medicine, Manchester Academic Health Science Centre, Central Manchester University Hospitals NHS Foundation Trust, Manchester, UK,

^bCentre for Human and Clinical Genetics, Leiden University Medical Centre, Leiden, The Netherlands, ^cIstituto di Farmacologia Traslazionale del CNR, Rome, Italy, ^dDepartment of Human Genetics, University of Leuven, Leuven, Belgium, ^eInternational Huntington Association, c/o Huntington's WA (inc) The Niche, 11 Aberdare Road, Nedlands, 6009, Western Australia, Australia, ^fNeurological Department, Fundación Jiménez Díaz Avda, Reyes Católicos, 2 28040, Madrid, Spain, and ^gDepartment of Neurology Leiden, University Medical Centre, PO Box 9600, 2300RC, Leiden, The Netherlands

^tEHDN WG Genetic Testing and Counselling: Emilia Bijlsma, Ellen Blinkenberg, Yvonne Bombard, Pascal Borry, David Craufurd, Mary Davis, Christine de Die-Smulders, Claudia Downing, Alexandra Dürr, Maria Garcia Barcina, Ruth Glew, Arvid Heiberg, Frances Heydon, Dorota Hoffman-Zacharsk, Ulrika Hösterey Ugander, Maria José Trujillo Tiebas, Wioletta Krysa, Inge Liebaers, Christiane Lohkamp, Paola Mandich, Caterina Mariotti, Bea De Schepper, Emilio di Maria, Andrea Nemeth, Oliver Quarrell, Pascale Ribai, Alicia Semaka, Sara Seneca, Jorge Sequeiros, Ferdinando Squitieri, Anna Sulek, Lucienne van der Meer, Christine Verellen-Dumoulin, Guido de Wert.

[‡]Editorial committee: Martin Delatycki, Mark Guttman, Michael Hayden, Martha Nance, Fiona Richards, Louise Vetter.

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Corresponding author: Dr Rhona
MacLeod, Genetic Medicine,
Manchester Academic Health Science
Centre, Central Manchester University
Hospitals NHS Foundation Trust,
Manchester, UK.
Tel.: +44 161 276 6510;
fax: +44 161 276 6145;
e-mail: rhona.macleod@cmft.nhs.uk

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The 1994 predictive test guidelines for Huntington’s disease (HD) were published by an *ad hoc* Committee comprising representatives from the World Federation of Neurology (WFN) and the International Huntington Association (IHA) (1, 2) shortly after the gene mutation for HD was identified. These guidelines have led the way in setting standards for predictive testing not only for HD, but also for other late onset neurodegenerative diseases such as familial frontotemporal dementia and spinocerebellar ataxias (SCA’s). They were also a valuable foundation for good clinical practice for predictive testing for hereditary cancers and other late onset conditions. Having a clear set of recommendations has helped to clarify the predictive test process for both clinicians and family members. Undoubtedly the guidelines have succeeded in their original aims of setting minimum standards for predictive testing, protecting at risk individuals and providing a reference point to help with ethical and clinical dilemmas as they arose. Whilst it is essential after twenty years to review the guidelines in the context of the substantial evidence that has emerged in the intervening years, many of the recommendations remain valid today.

The process of reviewing the guidelines was initiated by the European Huntington Disease Network (EHDN) ‘Genetic Testing and Counselling’ Working Group, formed during the EHDN congress in Dresden in 2007 by Prof Gerry Evers-Kiebooms. The aim of the working group (WG) was to look at communication in relation to genetic test information. Members of the WG include family members, genetic counsellors, psychologists, clinical geneticists, neurologists, and laboratory scientists from over 12 European countries. During the first WG workshop in Leuven (BE) in 2008, attention focused more on the predictive test guidelines. Whilst there was consensus that the guidelines were an excellent and valued resource, gaps were apparent in relation to new evidence and practices that had emerged since 1994. These included new technology such as preimplantation genetic diagnosis (PGD), increased scientific knowledge about HD (understanding of intermediate (IA) and reduced penetrance (RP) alleles, and prodromal signs), the debate surrounding the testing of minors,

new opportunities to participate in research and data on individuals’ experiences of testing such as post test discrimination.

Subgroups were set up to review the current research evidence in relation to six sections of the original guidelines that corresponded to the identified gaps (2.1 Testing of minors; 2.8 Laboratory standard of accuracy; 4.0 Communication of information; 5.2 Information pertaining to the test 7.0 ‘Prenatal Diagnosis’ renamed ‘Reproductive options’; 9.0 Post test counselling). The sub-groups comprised WG members with a particular specialism and/or interest in the topic. Family members participated in each of the sub-groups and international participants outside Europe were invited to contribute their expertise on specific topics. Written proposals, debated in plenary discussions, included the rationale for changes and references used by the sub-group. The sub-group members subsequently corresponded by email and drafted updates and additions to the original guidelines.

The proposed changes have undergone a lengthy consultation process both through the EHDN website (June–August 2010), where comments to the proposed changes could be posted, and globally through a review from a committee appointed jointly by IHA and WFN (Nov 2010–June 2011). A Town Hall session at the World Congress Meeting on HD in Melbourne in September 2011 provided a forum for the proposals to be presented to the wider HD community. This proved a valuable source of feedback and also drew on the knowledge and input of an expert panel of professionals and family members from countries including South America, Australia and Canada. Following the meeting in September 2011 Prof Raymund Roos, Chair of the WFNHD Research Group, invited a small editorial committee, drawn from the international community, to assist with the final edits.

A proposal made at the 2011 World Congress Meeting on HD was for the guidelines to be reviewed every two years in conjunction with the World Congress meeting. Prospectively this will allow all members of the HD community to put forward points for consideration by a committee appointed on behalf of the

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Chairs of both the IHA and WFNHDRG. This will also ensure that clinical recommendations continue to evolve and reflect changes in our knowledge and practice.

The document that follows is the next version of the 1994 predictive test guidelines for HD. It is important to emphasize that these are not intended as rigid rules but rather recommendations to guide and inform practice, based on current evidence and expertise.

Finally it is hoped that these proposals will stimulate new discussion about predictive test counselling approaches and how best to serve the needs of individuals and families. New challenges continue to arise in predictive test counselling; for example, how to ensure equity of access to genetic counselling services and how to ensure a new generation of young people from HD families have their say in the way genetic counselling services are provided.

1. Recommendations (REC) and comments (COM)

REC 1

All persons who may wish to take the test should be given up to date, relevant information in order to make an informed voluntary decision.

COM 1

The highest standards of counselling should be available in each country. It is recommended that informed consent for the test be documented with the signature of the person to be tested and the professional responsible for the counselling as a standard medical practice.

2. Access to the test

REC 2

The decision to take the test is the sole choice of the person concerned. No requests from third parties, be they family or otherwise, should be considered.

COM 2

The person must choose freely to be tested and not be coerced by family, friends, (potential) partners, physicians, insurance companies, employers, governments, etc.

REC 2.1

It is recommended that the minimum age of testing be 18 years. Minors at risk requesting the test should have access to genetic counselling, support and information including discussion of all their options for dealing with being at risk.

COM 2.1

Testing for the purpose of adoption should not be permitted, since the child to be adopted cannot decide for him/herself whether he/she wants to be tested. It is essential, however, that the child should be informed about his/her at-risk status.

Reasons for the changes 2.1

- (1) Although some authors were in favour of a less restrictive recommendation for testing minors on the basis of potential beneficial rather than harmful effects (3–5), a cut-off age for the

access to the test was deemed necessary on the basis of a principle of precaution, in the absence of reliable evidence on the benefits and harms of testing minors.

- (2) The age of majority appeared to be a weak criterion, since it varies between countries (e.g. medical majority 15 years in Denmark, 16 years in Lithuania, 14 years in Portugal, 15 years in Slovenia, 16 in Spain). Also, the right acquired at a particular age (e.g. legal versus medical majority) differs between countries. Although arbitrary, a specific cut-off age (18 years) was considered to be a better criterion.
- (3) A recommended minimum age is more in keeping with the literature that has looked at the issues involved in the testing of minors (6–8). The new recommendation is intended to allow a more individualized approach to adolescents requesting the test (8–10).
- (4) A clinical recommendation was proposed to offer counselling to adolescents requesting the test, instead of denying it outright.

REC 2.2

Each participant should be able to take the test independently of his/her financial situation.

COM 2.2

Each national lay organization should use its influence with government departments, public and private health insurers, etc, to reach this goal.

REC 2.3

Persons should not be discriminated against in any way as a result of genetic testing for Huntington's disease (see also REC 5.3.5).

REC 2.4

Extreme care should be exercised when testing would provide information about another person who has not requested the test.

COM 2.4

This will arise when an individual(s) at 25% risk request(s) testing with full knowledge that his/her parent does not want to know his/her status. Every effort should be made by the counsellors and the individuals concerned to come to a satisfactory solution of this conflict.

REC 2.5

For participants with evidence of a serious psychiatric condition, it may be advisable that testing is delayed and support services put into place.

REC 2.6

Testing for HD should not form part of a routine blood investigation without the specific permission of the subject.

COM 2.6

Such a specific permission should in principle also be required for symptomatic persons.

REC 2.7

Ownership of the test results remains with the person who requested the test. Legal ownership of the stored

DNA remains with the person from whom the blood was taken.

COM 2.7

The consent form should address this issue. Local legal opinions may be helpful.

REC. 2.8

All laboratories are expected to comply with the Organization for Economic Co-operation and Development (OECD) Guidelines for Quality Assurance in Molecular Testing by providing and practicing genetic testing under a quality assurance framework, meet rigorous standards of accuracy, participating in external quality assessment (EQA) schemes and working towards certification and accreditation.

COM 2.8

At-risk individuals, family members and the lay organizations can enquire about the quality standards of the laboratory, including, for example, its certification and accreditation status. The lay organizations can also assist persons who want to be or have been tested with their enquiries and concerns.

REC 2.8.1

Laboratories should be cognizant of the limitations of the methodologies used (including, e.g. the possibility of missing a very large expansion, the risk of error that might lead to a non-carrier result if an affected relative has not been tested), and should indicate these clearly in reports issued, along with margins of error.

Reasons for the changes 2.8 and 2.8.1

- (1) Since 1994 several guidelines for best laboratory practice in genetic testing have been issued.
- (2) Quality control and accreditation of laboratories have become essential requirements since 1994.
- (3) One of the basic principles according to the OECD guidelines (11) is that predictive genetic tests should be accompanied by genetic counselling, and laboratories should ensure that this is the case.
- (4) Several limitations and an error estimate of CAG repeat sizing have been reported in the last 15 years (12–15), which should be mentioned in the report.

REC 2.9

The counsellors should be specifically trained in counselling methods and form part of a multidisciplinary team.

COM 2.9

Such a multidisciplinary team should consist, for example, of a clinical geneticist, genetic counsellor or social worker, neurologist, psychiatrist or psychologist.

3. Support during the test process

REC 3

The participant should be encouraged to select a companion to accompany him/her throughout all the

different stages: the pre-test, the taking of the test, the delivery of the results and the post-test stage.

COM 3

This should be assessed on an individual basis and the presence of a companion may not be appropriate or required in all cases.

REC 3.1

The counselling unit should plan with the participant a follow up protocol which provides support during the pre- and post-test stages, whether or not a person chooses to be accompanied by a companion.

COM 3.1

Wherever possible, support should be available close to the person's community, and on a remote basis, by phone or telehealth where necessary.

4. Recommendation on communication of information

REC 4

Testing and counselling should be provided by genetic counselling units knowledgeable about molecular genetic issues in Huntington's disease. These centres should work in close collaboration with the lay organization(s) of the country.

COM 4

Often the test will be conducted at a site different from the counselling centre. If no lay organization exists in the country, the centre should contact the IHA.

REC 4.1

The laboratory performing the test should not communicate the final results to the counselling team until very close to the time the results are given to the participant.

COM 4.1

The aim is to protect the participant from the possibility of counselling bias at any time (see also COM 5.2.6).

REC 4.2

As a rule, members of the counselling team or the technical staff should not communicate any information concerning the test and its results to third parties without the explicit permission of the person tested.

COM 4.2

Only in the most exceptional circumstances (e.g. prolonged coma or death) may information about the test result, if so requested, be provided to family members whose risk is affected by the result.

REC 4.3

Neither the counselling centre nor the test laboratory should establish direct contact with a relative whose DNA may be needed for the purpose of the test without permission of the participant and of the relative. All precautions should be taken when approaching such a relative.

REC 4.4

Care should be taken regarding access to clinical reports of the test results.

COM 4.4

Consent of the participant should be sought before sending a letter to any physician involved in their care (e.g. family doctor, neurologist, or hospital physician). The possible benefits and drawbacks of sending the result to such physicians should be discussed. These

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benefits include: post-test support, future clinical care including identification and support around the onset of symptoms, and their symptomatic treatment. The risks include: potential discrimination in economic, social and medical domains, should their medical files be accessed by third parties.

In general, it is good clinical practice for the counselling team to suggest that other physicians involved in the participant's care be kept informed about the test and the result. If the participant objects, his/her view should be respected except in the most exceptional of circumstances. If consent is given by the person tested for the test result to be communicated it should be accompanied by a full explanation of the meaning of that result.

Reasons for the changes 4.2 and 4.4

- (1) Participants should be asked for their consent before sending a letter to their family physicians, as they may experience discrimination in economic, social, and medical domains should their medical files be accessed by third parties in the future.
- (2) There is evidence to suggest that participants sometimes take the initiative and request that letters are not sent to the family physicians (16).
- (3) Although some clinics have taken upon themselves not to send letters to the family physician (17), this is not uniform practice.

5. Essential information

COM 5

'Essential information' means information which is absolutely vital to the whole test procedure.

5.1. General information

COM 5.1

This information should be both written and oral and be provided by the team responsible for the test service.

REC 5.1.1

On Huntington's disease, including the wide range of its clinical manifestations, the social and psychological implications, the genetic aspects, reproductive options, availability of treatment, etc.

COM 5.1.1

It must be pointed out that at this time no proven prevention, treatment that slows disease progression, or cure is available.

REC 5.1.2

On the implications of non-paternity (and non-maternity).

COM 5.1.2

Genetic testing may show, or suggest, that the putative parent is not the biological parent; this aspect should be drawn to the attention of the participant and discussed. With the presently available techniques of *in vitro* fertilization, etc., even occasional non-maternity may occur.

REC 5.1.3

On lay organizations, including their documentation on HD, their addresses for help and social contacts, etc.

COM 5.1.3

If no lay organization exists in the country, contacts can be made with the IHA or lay organization of a neighbouring country.

REC 5.1.4

Psychosocial support and counselling must be available before the test procedure commences.

COM 5.1.4

Lay organizations should be mentioned as an additional source of support and information.

5.2. Information pertaining to the test

REC 5.2.1

How the test is done.

REC 5.2.2

Possible need for DNA from an affected family member and the possible problems arising from this.

COM 5.2.2

Asking an affected person, who may be unaware of or unwilling to acknowledge his/her symptoms, to contribute a blood sample may be an invasion of privacy.

REC 5.2.3

The limitations of the test (error rate, uncertain predictive interpretation of some CAG repeat numbers, etc).

REC 5.2.4

The counsellor must explain that, although the genetic mutation has been found, at the present time only limited useful information can be given about age at onset or about the kind of symptoms, their severity, or the rate of progression.

COM 5.2.4

The correlation between CAG repeat size and mean age of onset could be discussed, but it is important to point out the wide confidence intervals. A specific repeat size is usually associated with a wide range of age at onset; current mathematical models of age of onset have not been validated for clinical practice.

Reasons for the changes 5.2.4

- (1) Prediction models of age at onset based on (CAG)_n size have evolved in the last few years (18–21).
- (2) Although an initial validation of these models has been reported, they might not be free from biases (21).
- (3) These models do not include factors, beyond CAG repeat size, that have been shown to influence age at onset, such as genetic and environmental modifiers (22–25).
- (4) Although these models have an unquestionable value in research, it appears premature to use them in genetic counselling.

REC 5.2.5

Pre-test genetic counselling should mention all possible test outcomes, including intermediate and reduced penetrance results, which may be prone to repeat instability and may expand into higher repeat ranges upon transmission to future generations. However, there is insufficient information regarding the magnitude of the risk of expansion for future generations.

COM 5.2.5

There is at present insufficient information regarding clinical implications of intermediate alleles for future generations.

Reasons for the changes 5.2.5

- (1) Intermediate alleles (IA) and reduced penetrance alleles are known to be prone to expansion upon intergenerational transmission with a so far unknown probability (26–29).
- (2) The frequency of IA in the general population is relatively high (estimated 2–6%), and its possible implications should be mentioned in pre-test counselling (28–32).

REC 5.2.6

The predictive test indicates whether someone has or has not inherited the gene mutation, but it does not make a clinical diagnosis of HD if the gene expansion is present.

COM 5.2.6

Particular care should be taken with participants who are believed by the clinician to be showing early symptoms of HD; however, persons with evident but unacknowledged symptoms should not automatically be excluded from the test. Rather, they should be offered additional pre and post test support.

REC 5.2.7

Pre-test counselling should also outline information on post-test counselling and options for future research participation and care.

5.3. Information on consequences

REC 5.3.1

For the person him/herself.

COM 5.3.1

Most participants will adjust to their predictive test result. Some individuals may, however, experience difficulty coping with any of the possible results in the short or long term (including a result in the normal range). Additional counselling should be offered to those at risk of having difficulties with coping (e.g. individuals with a history of psychiatric illness).

REC 5.3.2

For the spouse/partner and children.

COM 5.3.2.

If the participant is not accompanied by his/her spouse/partner during the counselling sessions, there should be particular discussion about the potential

impact of the test result on the spouse/partner. It is possible that the genetic test result and/or family history will impact the participants' current or future family members' eligibility for insurance, employment, legal care of and access to children, and adoption.

REC 5.3.3

For the affected parent and his/her spouse.

COM 5.3.3

The feelings of the affected parent, who may well become aware of the results, must be taken into account.

REC 5.3.4

For the other members of the participant's family.

COM 5.3.4

Whatever information is obtained, it may influence the feelings of and the relationship with others, with a potential for discrimination in the family. This may include: disrupted patterns of behaviour and interaction, such as communication changes and feelings of altered sense of membership.

REC 5.3.5

Potential socioeconomic consequences, including employment, insurance, legal care of and access to children, adoption eligibility, social security, data security and other problems which may occur as a consequence of disclosing the test result or family history.

Reasons for the changes 5.3.1 and 5.3.5

- (1) The new comment 5.3.1 about the psychological effects of predictive testing was added in light of much evidence on this aspect (33–39).
- (2) The expansion of comment 5.3.2 highlights the possibility of the participant's family members experiencing discrimination because of the genetic test result or family history (40)
- (3) The expansion of comment 5.3.4 highlights the possibility of discrimination within the family, which has been reported in discrimination studies from US, Australia, and Canada (41).
- (4) Expansion of comments 5.3.2 and 5.3.5 was based on emerging evidence suggesting that individuals at risk experience discrimination and stigmatization in custody of and access to children, once separated from their spouse, and in adoption (42, 43).
- (5) Family history, more than genetic testing, appears to be the major reason for genetic discrimination in relation to Huntington disease (42–44).

5.4. Information on alternatives the participant can adopt

REC 5.4.1

Not to take the test for the time being.

REC 5.4.2

To deposit DNA for research.

REC 5.4.3

To deposit DNA for possible future use by family and self.

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REC 5.4.4

DNA deposited under 5.4 above would be made available to the donor's family members at their request after the death of the donor if it is essential to obtain an informative result.

REC 5.4.5

In the case of DNA deposited under 5.4.2 and/or 5.4.3 above, the unit collecting the DNA must provide a written declaration that samples will not be used for purposes other than specified in the said declaration with the exception of the provisions of 5.4.4.

6. Important preliminary investigations

REC 6.1

It is important to verify that the diagnosis of HD in the person's family is correct.

REC 6.2

Neurological examinations (if possible) and psychological appraisal are considered important to establish a baseline evaluation of each person. This however is not a requirement for participation in predictive testing.

COM 6.2

Refusal to undergo these and other additional examinations will not justify the withholding of the test from participants.

7. Reproductive options

REC 7.0.1

Preconception counselling should be available to couples where one partner is at risk of HD or is a carrier of the HD gene expansion.

COM 7.0.1

The importance of preconception counselling is stressed, because of the timeframe in making a decision about testing during an ongoing pregnancy. Moreover, such preparation may help to decrease the simultaneous requests for presymptomatic and prenatal diagnosis; a very stressful situation due to the limited time available and the potential for consecutive adverse outcomes.

REC 7.0.2

Preconception counselling should include discussion around the range of reproductive options available. These options may include proceeding with a pregnancy without testing, prenatal diagnosis (PND) preimplantation genetic diagnosis (PGD), donor insemination and adoption.

7.1. Prenatal diagnosis (PND)

REC 7.1.1

Couples should be made aware of all the options available to them in pregnancy, including the possibility of prenatal testing.

COM 7.1.1

Careful pre-test counselling by an informed professional is necessary in order to ensure that the (future) pregnant woman and her partner are fully aware of the

consequences of prenatal testing. All possible test outcomes (full expansion, reduced penetrance, intermediate and normal alleles) should be made clear to the couple. It is preferable for the counselling to take place in a specialized (prenatal or genetics) centre.

REC 7.1.2

Direct prenatal testing for the HD mutation is usually only performed if the parent at risk has already been tested. For a possible exception see 7.1.6.

REC 7.1.3

PND for an individual with a reduced penetrance allele of the HD gene is justified.

REC 7.1.4

PND for an individual with an intermediate allele of the HD gene is justified.

COM 7.1.4

There is insufficient information regarding the magnitude of the risk of CAG repeat expansion of intermediate alleles in the transmission to offspring. The risk of expansion into the full penetrance range is small, but may vary with the CAG size of the intermediate allele and the ethnicity of the individual.

REC 7.1.5

Exclusion PND should be available as an option for couples where the at-risk parent does not want to know his/her genetic status. The pros and cons of this procedure, however, should be discussed in detail during counselling.

COM 7.1.5

The major advantage of exclusion PND is that it allows the possibility of a prenatal test where the at-risk parent does not wish to have a predictive test but where the couple is clear they do not wish to have a child at risk of HD. The disadvantage is that the couple may end up terminating an unaffected pregnancy where the at-risk parent is not a mutation carrier.

REC 7.1.6

Direct prenatal testing of the fetus where one of the parents is at risk but prefers not to know his/her carrier status should be considered where the couple requests this in pregnancy.

COM 7.1.6

The only advantage of this approach is that, in the case of a normal result in the fetus, the parent at risk still does not know his/her carrier status, preserving his/her wish not to know. However, in the case of identifying the gene mutation in the fetus, the carrier status of the parent at risk will be disclosed. The possibility of this adverse outcome should be clearly outlined and the couple adequately prepared for such an eventuality, before agreeing with this test proposal.

REC 7.1.7

The couple requesting prenatal testing must be clearly informed that if they intend to complete the pregnancy whether the fetus is a carrier of the gene expansion or not, there is no valid reason for performing the test.

COM 7.1.7

This is in line with the recommendation not to test minors. The child's autonomy regarding his/her future right to decide whether or not to undergo

a pre-symptomatic test is violated if pregnancy is continued in the case of an abnormal prenatal test result.

The limiting of the couple's autonomy and their right to freely decide on the action taken on the basis of the prenatal test result should be explained and clarified with respect.

Also, there is a small, but not negligible risk of spontaneous abortion related to the procedure.

REC 7.1.8

It is not recommended to terminate the pregnancy of a fetus on the basis of an intermediate allele result.

COM 7.1.8

An allele in the intermediate range is not associated with HD symptoms. Although an intermediate allele can expand into a reduced penetrant or full penetrant allele in future generations, this fact per se is not a reason for a pregnancy termination.

Reasons for the changes Section 7.1

- (1) Since 1994 the practice of prenatal diagnosis has been changed considerably and there is much more experience with prenatal testing (45, 46)
- (2) Some recent papers raise difficult ethical issues (47–50)
- (3) New techniques such as non-invasive testing of fetal DNA in the maternal blood, are the subject of research but are not yet available for clinical use (51).

7.2. Preimplantation genetic diagnosis

COM 7.2

Preimplantation Genetic Diagnosis (PGD) in association with IVF is a reproductive option for people at risk of passing on a genetic condition. The different types of PGD for HD and the different situations where PGD may be an option will be outlined in the following specific recommendations regarding PGD for HD.

REC. 7.2.1

It is recommended to offer PGD to an asymptomatic carrier of the HD gene expansion (36 or more repeats) and his/her partner if there is access to this technology in the country where genetic counselling is being provided.

COM 7.2.1

In general, PGD is offered to people at risk of passing on a serious genetic condition. The risk of expansion of an intermediate allele to a reduced penetrant or full penetrant allele is not exactly known, but is low. Participants with an intermediate allele requesting PGD should be offered genetic counselling.

REC. 7.2.2

Exclusion PGD should be available for couples at high risk for offspring with HD.

COM 7.2.2

The major advantage of exclusion PGD is that it enables prospective parents to avoid the transmission of the

HD mutation, while at the same time respecting the at-risk person's wish not to know. The counselling should explicitly address the impact of the parent's remaining uncertainty about his/her own genetic status upon the welfare of the future child(ren).

REC. 7.2.3

Non-disclosure PGD should be discouraged.

COM 7.2.3

Non-disclosure PGD raises troubling practical and ethical issues. First, in practice it will be extremely difficult to preserve the participant's wish not to know. Second, the procedure creates difficult situations where reproductive physicians would be obliged both to offer more IVF/PGD cycles and to perform a sham transfer while the risk of having a child with HD will be (practically) zero.

REC. 7.2.4

Couples where one partner is already symptomatic should have access to counselling for PGD. Psychosocial counselling on the impact upon a child of growing up with a parent with HD in general and exploration of the potential effects in the specific case is an important aspect of the PGD procedure.

COM 7.2.4

Being symptomatic is not a priori an exclusion criterion for PGD. Special attention should be given to the effects of the symptoms of HD upon the future child's welfare. The condition and coping skills of the partner are crucially important in this regard. A case-by-case approach does optimal justice to couples where one partner faces the personal burden of HD in her/himself, while being aware of the ramifications for future children.

REC. 7.2.5

Only embryos with two normal HD alleles should be transferred.

Reasons for adding Section 7.2

- (1) Since 1998 Preimplantation Genetic Diagnosis (PGD) has become one of the reproductive options for couples at risk for Huntington's disease (52, 53).
- (2) Although general PGD guidelines exist (54), no specific guidelines are available for Huntington's disease.
- (3) PGD may be performed in different ways: direct, exclusion, non-disclosure (55–57).
- (4) Given the complexity of PGD techniques and their ethical implications, some risk situations require particular attention.

8. The test and delivery of results

REC 8.1

Excluding exceptional circumstances there should be a minimum interval of one month between the giving of the pre-test information and the decision whether or not

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to take the test. The counsellor should ascertain that the pre-test information has been properly understood and should take the initiative to be assured of this. However, contact will only be maintained at the participant's request.

COM 8.1

Such an interval is necessary to give the person sufficient time to assimilate the pre-test information in order to make an informed decision. During this interval, specialists from the test centre must be available. Prenatal testing may represent an exception, as it is important to complete testing procedures as early as possible during the pregnancy.

REC 8.2

The result of the predictive test should be delivered as soon as reasonably possible after completion of the test, on a date agreed upon in advance between the centre, the counsellor, and the person.

REC 8.3

The manner in which results will be delivered should be discussed between the counselling team and the person.

REC 8.4

The participant has the right to decide at any time that the result shall not be given to him/her.

REC 8.5

The results of the test should be given personally by the counsellor to the person and his/her companion. In geographically remote areas the result session may be arranged by prior agreement with a clinician known locally to the participant. No result should ever be given by telephone or by mail. The counsellor must have sufficient time to discuss any questions with the person.

REC 8.6

All post-test provisions (see Section 9) must be available from the time the test results are given.

9. Post-test counselling

REC 9.1

The frequency and the form of the post-test counselling should be discussed between the team and the participant before the performance of the test, but the participant has the right to modify the planned programme. Although the intensity and frequency will vary from person to person, post-test counselling must be available at all times.

REC 9.2

The counsellor should have contact with the person within the first week after delivery of the results, regardless of the test result.

REC 9.3

If there has been no further contact within one month of the delivery of the test result, the counsellor should initiate the follow up.

REC 9.4

It is essential that post-test counselling is made available regardless of the person's financial situation.

REC 9.5

During post-test contact specific information on follow-up options, including (if applicable) participation in clinical research studies, can be provided. The nature

of emerging prodromal signs of pre-motor manifest mutation carriers and their management possibilities (if available) could be discussed.

COM 9.5

Information should be provided on:

- specialist centres providing clinical care for HD
- provision for regular follow up after the test
- option of participation in observational studies (e.g. REGISTRY, Enrol-HD)
- option of participating in future clinical trials
- there is a pre-motor stage of HD that results in symptoms and signs likely reflecting HD-induced brain changes ('prodromal' signs)
- prodromal signs and symptoms might respond to symptomatic pharmacotherapy, even if no reliable data on this point are available at present.

Participation in research is entirely voluntary and the standard of follow up care provided will be unaffected by whether or not the individual chooses to take part.

Reasons for the changes 9.5 and 9.7

- (1) Interventional studies (trials) are on the horizon (58–60), although no definite timelines for the start of such trials is available.
- (2) Results from the PREDICT and TRACK studies have provided evidence for pre-motor signs and symptoms ('prodromal' signs) and demonstrated the feasibility of clinical studies in this population (61–64).
- (3) Empirical evidence suggests that some of the prodromal signs, such as depression and mood disorders, might be symptomatically treated.

REC 9.6

Ideally, information in Section 9.5 should be raised during the pre-test counselling.

REC 9.7

The lay organization has an important role to play in the post-test period. The information and support that it can provide should always be offered to the participant regardless of whether he or she belongs to that organization.

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