Presymptomatic DNA Testing in BRCA1/2

Invited reactions from the field on the van Oostrom and Tibben paper

The editors of this journal have approached a number of geneticists and genetic counsellors from different countries to obtain their comments on the paper by van Oostrom and Tibben which appeared in a recent issue of the journal (2004; 2 (1):19-23). In this paper, the authors proposed a simplified procedure for presymptomatic testing of BRCA1/2 mutations, which departs from the "Huntington-model". Although the editor's survey was not designed to give a representative overview of international approaches towards presymptomatic testing for BRCA1 and 2 mutations, it *does* give the readers a flavour of the findings and concerns of some of our colleagues from the field and highlights some of the similarities and differences between current practices in different clinics. We do not fully reproduce all comments here, but rather quote and summarise selectively the most illustrative remarks and have asked van Oostrom and Tibben for a response.

Steven Narod, University of Toronto, Canada, agrees to use a more a simplified procedure. He reports that their department sends out paperwork (pedigree forms and information by mail) about the test design. They have one pre-test session with their patients and take blood at that time; test results are given 6 months later. If the patient wishes they can defer testing or be offered a second pre-counselling session. Currently, 80% of their patients get their blood taken for testing at the first appointment, 10% defer and give blood at a later appointment and 10% decline testing.

Jill Stopfer, responding on behalf of the University of Pennsylvania, USA, breast/ovarian cancer genetics clinic (Barbara Weber, Timothy Rebbeck), reports that their present testing procedures are similar to those proposed by van Oostrom and Tibben. The patients typically meet first with a genetic counsellor or genetic nurse for pedigree assessment, risk counselling, and pre-test counselling, if appropriate. They return for a second visit with a physician at which point an exam is done, risk assessment further discussed along with medical recommendations and blood is drawn for testing. Results are offered either in person, or as part of a scheduled phone appointment if preferred by the patient.

Annika Lindblom, from Karolinska Institutet, Sweden, reports that the model suggested by van Oostrom and Tibben is in agreement with what her department is currently doing. As a routine they have one pre-test counselling session and one post-counselling session where they offer (and usually it is accepted) referrals to breast-gynaecological check-up programmes. They also offer consultations with breast surgeons and a psychologist. Most often this is not accepted at that time by the patients, but at a later stage it is. They always offer carriers a third follow-up visit after the test, which is most often declined. The patients also get informed that they are always welcome to contact their department in person, by telephone or via letter. Their impression is that this is normally satisfactory. Initially they had more strict procedures and also protocols for short and long time follow-up but do not think that it is necessary any more, which, they believe, is to some extent due to the increased knowledge about BRCA1-2 and familial breast cancer in the general population. Their experience will be reported in a paper (Arver et al, Genetic testing, *in press*).

Věra Krutílková, Věra Franková and Petr Goetz from Charles University, Prague, Czech Republic, report that in their department all patients undergoing the genetic testing receive at least two genetic counselling sessions (pre- and post-test). If they feel more extensive counselling would be needed, patients are encouraged to undergo another counselling session before or/and after the test. During the first counselling session patients are informed about the possibility to use the service of an associated psychologist and receive his/her telephone number. They stress that patients should have the possibility to contact a professional psychologist at any time during and after the testing procedure. Most of their patients (80%) retrospectively, did not feel during and/or after the testing the need for professional psychological help. Only 6.5% of patients used the service of a psychologist. The indications mentioned by van Oostrom and Tibben for the second counselling session with a genetic counsellor or psychosocial worker would in their opinion be difficult for the genetic counsellor to assess. The mandatory inclusion of another session with a psychosocial worker into the testing protocol could result into the prolongation of the pre-test period and therefore also the prolongation of the initiation of appropriate preventive care. For these reasons they think that inclusion of another counselling

session in a pre-test period is not appropriate unless requested by the patient. In their experience, long-term follow-up for mutation carriers is needed and highly appreciated by some patients (30%).

Gareth Evans from St. Mary's Hospital in Manchester, United Kingdom, reports that they do not insist on 3 sessions, but a minimum of two. It depends on patient knowledge, a period of reflection and how certain they are about going ahead.

Pål Møller from the Radium Hospital in Oslo, Norway, reports that their department uses a simplified procedure as well, however he believes that an international study on current testing practice would be useful in defining the best practice.

Andres Metspalu from University of Tartu, Estonia, agrees that leaving the Huntington model and adopting a simplified model for BRCA1/2 testing is important and would be beneficial for patient welfare.

Håkan Olsson from University Hospital of Lund, Sweden, reports that in Sweden counselling and testing in a presymptomatic setting follows the Huntington model, whereas for cancer patients the simplified procedure (table 2 in the van Oostrom/Tibben paper) is closest to practice. He reports that they have very good experience using those models.

Dieter Lohmann from Universtiätsklinikum Essen, Germany, reports on his experience with retinoblastoma gene testing and concludes that a two-step protocol is certainly sufficient for hereditary forms of the disease.

Pavel Elsakov from the Lithuanian Oncology Center points to the fact that in some countries and institutes, due to limited finances and inexperience (starting facilities), women may have to wait a long time before test results become available and will often postpone final risk classification to take advantage of the appropriate clinical treatment. Increased counselling sessions are likely to increase psychological stress in the women involved. Doctor Elsakov suggests that this should be studied and appropriately addressed in countries/institutes that face this particular problem.

Ewa Grzybowska from the Cancer Center in Gliwice, Poland, opts for two-session counselling for HBOC families. In her experience as a genetic counsellor, most of the patients coming to a genetic counselling unit think that one session is enough for all explanations and would be disappointed very much if she asked them to come couple of months later to take the blood sample for test.

Pilar Nicolás, University of Deusto, Spain, wishes to add an ethical and (international) legal perspective to the discussion, underlining the fact that to carry out the genetic analyses as part of appropriate genetic counselling is an obligation established in the international framework with a moral or judicial binding character. The following international authorities that have defined ethical and legal aspects of genetic testing procedures and/or recommendations on its use are cited by Dr Nicolás:

1º. International Declaration on human genetic data. UNESCO (October 16, 2003) (http://portal.unesco.org/shs/en/ev.php-URL_ID=1882&URL_DO=DO_TOPIC&URL_SECTION=201.html)

Article 2. (definitions) "(xiii) and 1, which define genetic counselling, stress, its availability when genetic data are collected and the fact it "should be non-directive, culturally adapted and consistent with the best interest of the person concerned".

2º. The 25 recommendations on the ethical, legal and social implications of genetic testing (European Community) http://europa.eu.int/comm/research/conferences/2004/genetic/recommendations_en.htm).

Recommendation 9, which addresses the availability of genetic counselling (in the case of highly predictive genetic tests for serious disorders, the offer of specific counselling should be mandatory, and patients should be strongly encouraged to take advantage of it), educational aspects, exchange of experience at the European level and development of quality standards.

3º. Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (4.IV.1997) (http://conventions.coe.int/treaty/en/treaties/html/164. htm)

Article 12, which defines predictive genetic tests: "Tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling".

Dr Nicolás comments that these texts are the basis to develop concrete protocols that fix the conditions of the genetic counselling and the "appropriate" information that has to be given.

He also refers to article 5 of the Biomedicine Convention, which deals with the obligation to obtain informed consent when one wishes to carry out any intervention in health and stresses the freedom of the patient to withdraw consent at any time. It is stated that in addition to the medical and psychological issues, which

are discussed with the patients during the presymptomatic testing procedure, it is necessary to inform them of the implications for the rights of the patient and others (usually relatives). Discussion should include the use of the information obtained, the possibility of exercising the right not to know (article 10.2 of the Biomedicine Convention and article 10 of the UNESCO Declaration), possible relevance for insurance and employment, and the possible repercussion for the patient's relatives.

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Response by Tibben and van Oostrom:

The comments show that our model reflects the international clinical practice. Of course, as Nicolás emphasizes, the counselling should meet the standards of high care, and the outcome of international debates needs to be considered. Indeed, distinguished groups and institutions of high esteem have established guidelines for appropriate counselling procedures. We favour that guidelines or a model ought not to be used as a straitjacket but as a framework of recommended procedure for careful testing. Following the guidelines may also provide a safety net that comforts the test candidate and his or her companion. After 17 years of experience, most of the difficulties encountered in predictive testing relate not to laboratory issues, but to the human aspects of testing. People find it difficult to process the complex risk figures, to adopt the often far-reaching treatment or preventive options, and to consider life style changes. The great challenge is to find out how to support people in optimally processing the information that is available, how to enable them to make the best personal decisions, how to help them to adjust to the test outcomes and take the appropriate actions, and how to encourage them to adjust their behaviour to profit optimally from testing. Moreover, we should realize that just telling people that they are at risk of developing a disease is rarely sufficient to change behaviour.

We have noticed the reluctance in some comments with regard to psychological support (Lindblom; Krutílková et al). Indeed, psychological support should not increase the stress (Elsakov) or delay the testing unnecessarily (Krutílková et al). As the word "support" may cause a misunderstanding, we should differentiate between psychological assessment and psychological support. Psychological support is meant to help people to better prepare them on their way to disclosure, and to adjust more adequately after they have learned the test results. Before offering support, however, we need to assess the test candidate's vulnerabilities. It is our opinion that counsellors are the first who should be able to identify the vulnerable test applicants. In our experience, about 20% of the test candidates might need professional psychological help, which is similar to the estimation of Krutílková et al. We agree with them that the assessment of needs may be difficult for a counsellor. The lessons from psychological follow-up studies have expanded our knowledge of who are at risk for adverse reactions. In addition, tools should be developed that enable counsellors to identify those people that need referral to a psychiatrist, psychologist, or psychosocial worker.

As clinical genetics has adapted the non-directive tradition (Nicolás), one might argue that a test candidate can consider the offer of psychological support more or less voluntarily. In our opinion, however, refusal of the offer of additional assessment and support cannot be accepted if there are strong indications for future maladjustment. If a counsellor estimates that the consequences of his or her "treatment", i.e. genetic testing, go beyond the test candidate's capacities to cope adequately, he or she has the professional responsibility to account for that and take the appropriate actions, with the inclusion of – further – psychological assessment and support. In some cases, the offer of psychological consultation is therefore not free of obligation. Needless to say that the prudent and skilful communication of a referral to a psychosocial worker will increase the acceptability by the test candidate.

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