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Predictive testing for Huntington's disease

Aad Tibben

Centre for Human and Clinical Genetics, Leiden University Medical Centre, P.O. Box 9600, 2300 RC Leiden, The Netherlands

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Abstract

Worldwide, predictive testing for Huntington's disease has become an accepted clinical application that has allowed many individuals from HD-families to proceed with their life without the uncertainty of being at risk. International guidelines have extensively contributed to establishing counselling programmes of high quality, and have served as a model for other genetic disorders. Psychological follow-up studies have increased the insight into the far-reaching impact of test results for all individuals involved. Although the guidelines have served as a useful frame of reference, clinical experience has shown the importance of a case-by-case approach to do justice to the specific needs of the individual test candidate. Issues such as ambiguous test results, lack of awareness in a test candidate of early signs of the disease, non-compliance to the test protocol, or the test candidate's need for information on the relationship between age at onset and CAG-repeat require careful consideration. Receiving a test result is only one of the transition points in the life of an individual at risk; such result needs to be valued from a life-cycle perspective.

Keywords: Huntington's disease; Predictive testing; Life cycle

After the localization and identification, in 1983 and 1993, respectively, of the hereditary cause of Huntington's disease, HD-families and patient organizations looked forward to an improvement in their current life and future perspectives. Now, although a cure is still far ahead, the availability of predictive testing has affected the HD-community profoundly over the last two decades.

1. Uptake of testing

Although previous studies had predicted a rather high uptake between 50% and 80%, fewer individuals than expected found their way to the clinical genetics centre [35]. The percentage of those at risk who requested testing when approached by registries or testing centres varied from less than 4% in Germany, Austria and Switzerland to 24% in the Netherlands (see Table 1) [8,22,24,30,34,37,44,46]. It was suggested, and confirmed, that it was a resourceful self-selected group that participated in predictive testing [9,28]. Those who did take a test were found to have relatively high ego strength/resources [6,13]; this was also underscored by a world-wide study from Vancouver showing that in almost 6000 tested individuals no catastrophic events had been reported [1]. Those who decided not to be tested had more frequent expectations of untoward emotional reactions, showed more hopelessness than tested subjects, were more uncertain about their abilities to adequately cope with bad news, and had more often learned about HD and their own risk in adolescence [5,51]. On the other hand, the tested and untested groups did not differ with respect to level of anxiety, ego strength, and coping strategies used [11]. Therefore, bias seems to be involved in the estimation of adaptation in HD risk carriers.

2. Reactions to test results

Worldwide, a number of groups started psychological follow-up studies on the impact of test results. About 15 years experience was reviewed by several authors [3,18,35]. The most important reasons for requesting a predictive test were the relief of anxiety about developing HD and preparing for the future, together with the need for planning a family. At group level, the following observations were made: despite the strong motivation to have a test, the studies have demonstrated that the well being of the group of test applicants was – in general – not different from the general population before disclosure of the test results, and distress, if reported, remained within normal limits. After disclosure of the results, both identified carriers and non-carriers had difficulties in adapting to the test result, but at different moments in time. Distress experienced by carriers increased in the first weeks after the test result, but returned to baseline level within 1 year. The relief non-carriers expressed in the first weeks after receiving the result disappeared afterwards;

E-mail address: a.tibben@lumc.nl.

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Table 1
Uptake of predictive testing for Huntington's disease

Germany, Austria, Switzerland	<3–4%	Laccone et al. [30]
Australia	5%	Taylor [46]
France	5%	Goizet et al. [22]
Spain	13%	Solis-Perez et al. [44]
United Kingdom	18%	Harper et al. [24]
Canada	18%	Creighton et al. [8]
The Netherlands	24%	Maat-Kievit et al. [34]

they experienced most distress at 6 months. Within 1 year, non-carriers seemed to be somewhat less distressed than they were before test disclosure, but they had not developed more optimistic expectations for the future.

What we do know now is that the predictive test has become a widespread and broadly accepted clinical application. Moreover, Huntington's disease has received much media attention and has served as the paradigm for many other hereditary diseases for which predictive testing has become possible, such as breast and ovarian cancer, colon cancer, and cardiovascular disorders. The positive evaluation of predictive testing programmes for HD was at least in part thanks to the international ethical guidelines which were published in 1988 for the linkage test, and in 1994 for the mutation test [25].

Although families at risk had high expectations of the scientific progress that has led to the finding of the CAG triplet repeat mutation, there is still no immediate prospect of effective treatment. Given the lack of treatment options, test applicants often wish to have more information about the clinical meaning of the repeat number; this is understandable, because applicants take the test in order to obtain information about their future condition. In view of the evidence for a strong relationship between the number of CAG-repeats and the age of onset, applicants need more specific genetic information.

3. A closer look

As said before, predictive testing has not resulted in serious adverse events such as suicide or psychiatric illness, but this does not mean that predictive test subjects have not experienced any problems in adjusting to the test outcome. When we look more closely at clinical practice and take account of anecdotal evidence, we must admit that the published reports on tested groups require qualification at an individual level. Adjustment problems have been observed when individuals have found themselves forced to change their expectations and future intentions such as planning a family. Others have had no problems with the test result while it did not interfere with their current life; however, when life reaches certain transition points, such as the beginning of a long-term relationship, or when planning a family has become a major issue, identified carriers may feel blocked or frustrated in their future plans [4], and become fully aware of the significance of the test outcome for the first time. Also, the test result has in some cases led to the reactivation of (traumatic) experiences with regard to HD, stirring up a range of feelings and memories that were previously denied or repressed.

Individuals have also reported problems with adjustment when their relatives were not able to accept or appreciate the outcome, or when relatives denied or dismissed the result. Carriers were more likely to divorce in the first 6 months after disclosure than non-carriers [7,36,45,47].

Furthermore, people who had children had more problems in accepting an unfavourable result and more often felt guilty, compared with those who had no children. Individuals who became aware of early symptoms reported that this awareness confronted them for the first time deeply with their future prospects, as if the test result first sank in. Recent life events related to HD were the first time that many people truly realized the personal significance of their test result. Receiving a good result was problematic for some non-carriers if they had previously adopted a Huntington-identity. Consequently, the good result was difficult to assimilate; it took them time to get rid of a future with Huntington's disease.

Some carriers did not report having had depressive episodes in the post-test period, whereas their partners reported the opposite about them [49]. Moreover, test applicants were more defensive when filling out the MMPI than the general population, and female participants obtained a higher lie score than women in the general population [9].

DudokdeWit et al. introduced the possibility of assessing the manner in which participants discuss the disease, the test, and its implications in terms of coherence [17]. Coherence refers to the ability to discuss and to reflect upon emotions, feelings, and ideas without either becoming entangled in it or avoiding discussion of the subject. They found that one-third of the participants in their study spoke incoherently about their possible inherited disease, the majority of them (two thirds) using an avoidance (dismissing) strategy, one-third being entangled. It turned out that those showing avoidance reported fewer problems than those being entangled. Dismissing subjects generally have more psychological and psychiatric problems than others do [15].

These findings support the impression of clinicians and counsellors that a group of HD risk carriers who report themselves to be functioning well are in fact having difficulty with being aware of the impact of their experiences with HD on their lives, reflected in sustained emotional numbness [16]. When the reality of a situation is avoided, it cannot be integrated into one's personal life, which might lead to adaptation problems.

4. Predictive testing and partners

A few groups have given specific attention to the impact of testing and test results for couples [12,14,36,38,40,48]. The overall picture is that few adverse effects on couple relationships have been observed. In the short term, some partners were more depressed than carriers and they had more pessimistic expectations. Also, partners have reported less sexual satisfaction. Although they experienced more problems than their carrier-partners, they were also more reluctant to admit marital adjustment problems and consequently to seek help. Some couples have started their relationship with the full awareness that one of them is at risk for HD. If the non-HD

partner anticipates a future in which she or he will take care of the affected partner for altruistic or self-sacrificing reasons, a favourable test result might disturb the planned 'relationship scenario'. So, if the partner choice was incompatible with the test result, couples had to re-evaluate their relationship. In the long term, partners reported a lower quality of their relationship with carriers. About a third had changed their marital status. Partners showed inadequate, passive coping strategies, did not seek social support or showed adequate problem solving. Distress in partners might be the result of changed marital roles, reluctance to seek help and the refraining from mourning. On the other hand, professional caregivers have not recognized the grief about the test result and the future perspectives [12,14,42,43]. In the long term, partners reported that it was not the test that had an adverse effect on their relationship, but being at risk that had caused the damage. Partners also felt emotional distancing and reported loyalty problems, often leading to extra-marital affairs. Some have attributed this to the advent of the first symptoms, accompanied by obsession and emotional withdrawal [38,40]. Richards and Williams commented on what a good and well adjusted relationship should involve: partners frequently interact with one another, seldom disagree on important marital issues, communicate openly with one another, and resolve disagreements in mutually satisfactory manner.

In conclusion, at a group level predictive testing has resulted in a reduction of psychological distress and an improvement of well-being. At an individual level, the clinical lessons are that we need to pay attention to persons with low ego-strength and unspecified motivation [13]. Moreover, almost a quarter may experience adverse events in the first year after disclosure [2]. When approaching the expected age of onset, carriers may feel more pessimistic [50]. The optimistic reports must be considered with caution, as high proportions (>50%) were lost to follow-up. Timman et al. found more pre-test distress in those lost to follow-up [50]. Moreover, the dropout rates in most follow up studies are high. Information from relatives about the well-being of these dropouts suggest that those who declined participation in follow up research, both carriers and non-carriers, often have serious problems they do not want to disclose, indicating that risk carriers applying for the test may have more problems than the studies suggest.

A subgroup of both carriers and non-carriers have long lasting adaptation problems. Those reporting to be distressed before test disclosure most frequently had problems in adapting to the test result. Although wellbeing seemed to be independent of test outcome, wellbeing was related to having children, certain personality traits (ego strength, coping), and the subjective estimation of the number of years before onset of HD.

5. The international guidelines

The international guidelines have served the process of counselling and testing very well, underlining the fruitful collaboration of international lay organizations and the World Federation of Neurology research group on Huntington's disease [2,25,53]. Moreover, the guidelines have been referred to in many articles on other testing programmes. The guidelines have been supportive in daily clinical work and were certainly not intended to be used as a straight jacket or as a tool of authority. However, counsellors can refer in their work with test candidates to the guidelines as a framework for good clinical practice. Clearly, some of the following issues have been discussed through time.

6. The counselling programme

The revised guidelines [25] suggest that the counselling programme should comprise at least three pre-test sessions, i.e. a genetic counselling session, and a neurological and psychological evaluation. After the disclosure of test results several post-test sessions should be scheduled over a 2-year period. However, based on clinical experience and research reports, every counselling requires a case-by-case consideration. In principle, the autonomy of the applicant needs to be acknowledged and encouraged, even if he or she does not agree with the recommendations of the guidelines, such as involvement of a companion, or refuses to comply with follow-up sessions. While a case-by-case approach may safeguard careful counselling and testing, there is always a risk that counsellors who have been involved in the testing programme for many years may become complacent. Another problem is that many tested applicants are lost to follow-up.

7. The neurological examination

Guideline 5.2.5 states that every effort should be made to distinguish between diagnosis of HD clinical symptoms and identification as a gene-carrier, hence the suggestion to perform a neurological examination; however, we need to differentiate between a genetic (predictive) test result and a clinical diagnosis. When an individual at risk asks for a genetic test, he or she may not (yet) wish to learn whether symptoms are already observable. Indeed, we sometimes see a test candidate who is clearly affected but who shows a lack of awareness of early signs. When the applicant clearly does not wish to consider that he is possibly affected and that he might perhaps need a neurological consultation, we should appreciate such as a psychological defence. Given that he has opted for predictive testing, he may have made the first step towards an awareness that he is affected. In such a case, testing serves as the prelude to accepting the clinical diagnosis. Hence, to avoid such a test candidate learning inadvertently about his condition, his attitude towards a clinical diagnosis needs to be explored before a neurological examination.

8. Psychological or psychiatric examination

Guideline 6.2 refers to psychological and/or psychiatric screening, which is strongly recommended to prevent adverse emotional responses. Screening for psychiatric disorders may indeed be appropriate to delay testing, initiate psychiatric treatment and stabilise the patient's condition in such cases before proceeding with testing. However, what if the psychiatric condition is a result of being at risk? As relief from uncertainty is the most cited motive for requesting a test, we have often observed

that a test outcome, even if unfavourable, brought peace of mind. When an applicant is in psychiatric or psychotherapeutic treatment, predictive or confirmative testing may sometimes be considered as part of the treatment. In the absence of any alternative way of removing or circumventing the uncertainty about one's genetic condition, the test may be a way out of an unbearable life.

9. Predictability of impact of test results

According to the guidelines, the impact of good or bad results is difficult to predict. It is certainly true that we are never sure of how people will react to either test result, and it would be unfair and unprofessional to pretend we could in a counselling session either warn or reassure test candidates. Yet, it would also be unfair not to make use of the wide experience and knowledge that has been collected through the years from the follow-up studies. Indeed, risk factors have been identified, and perhaps the most important is that the impact of either test result is only slightly dependent on the outcome. How people do react is much more dependent on individual characteristics such as the baseline mood, ego strength, and coping strategies. If the baseline mood is normal instead of depressed, and reflecting strong ego functions, the test candidate will be better able to handle an unfavourable result. If his ability to cope with difficult situations is adequate, as demonstrated by the adequacy of coping with previous life events, the test candidate may rely on this when receiving the test results. Assimilating test results will be less difficult if the test candidate can rely on a stable, open and supportive family compared with someone whose family resents doing the test. If the test candidate is able to mobilize support of intimate friends this will also be highly beneficial when getting bad news. If the partner-relationship is of a stable quality, and both partners can mutually care for each other and reflect on their relationship and the alternative scenarios with regard to the test outcome, the chance is considerable that they will adequately deal with the test results. When an individual has achieved independence from his family of origin, and feels consequently that the results have to be worked through by himself without obligation to his parents and siblings, he will very probably be better off then someone who has not psychologically separated from his parents. Last, but not least, if the applicant shows a willingness to engage in counselling, is open to the suggestions of the counsellor and his partner, and is willing to attend follow-up sessions, he is probably more self confident than someone who rejects any consideration.

10. Ambiguous test results

We know that 40 CAG repeats or more will definitely result in HD. However, test candidates who are found to have 35–39 repeats will be unsure whether they will develop HD or, if they get HD, to what degree. Those who are found to have 27–35 repeats will be fairly certain not get HD, but there is a small risk that their (future) children will inherit an allele that has expanded into the HD range. No data have been published about how people have assimilated a reduced penetrance or intermediate allele, but from other fields in genetics we know that people find it hard to understand complex risk figures without clear-cut implications. Anecdotal data have shown that, despite sound counselling and follow-up, applicants tend to underestimate a reduced penetrance result and may even consider this as a favourable result. Moreover, others who receive an intermediate allele result may perceive their result as worse than it is. This may be particularly the case when applicants have done the test to inform their children about their risks. An intermediate result provides both relief and worries at the same time. Needless to say, such results should not be underestimated and follow-up of this group is highly recommended.

11. CAG-repeat and age of onset

An inverse relationship between age at onset and repeat length has been clearly demonstrated [31,32] but this association is not sufficient to be used clinically to predict age at onset in individual cases. However, this knowledge has reached the families at risk and, understandably, they wish to make use of this relationship to give meaning to their own CAG-repeat length. Test candidates ask for the test in order to be better prepared for the future and to be able to make the appropriate adjustments. Some centres do not, or are reluctant to provide data about repeat length, except in case of intermediate or reduced penetrance alleles, while others give the data on the applicant's request. The lower the repeat length, the more reassuring the test outcome will be perceived to be. This perception is certainly not justified and needs to be discussed, recognising that people look for something to hold on to, no matter how (un)realistic this is. Although the guidelines (5.2.4) suggest that no information can be given about the age at onset, symptoms, severity, rate or progression, it is debateable whether people should be given access to these data with the caveat that the data are not very reliable. Indeed, on the one the hand people might be unable to handle complex risk data with uncertain clinical significance, while on the other hand getting these data might enhance the feeling of control over personal life and future. People ask for CAG-repeat length: there is a professional's duty to inform and a patient's right to get information. Another argument in favour of providing the repeat length is that given their need for information and the lack of treatment options in the near future, there is nothing else to offer individuals at risk other than greater control over their future. Further research with carriers may well reveal new data regarding timing of onset in the life cycle, modifiers of age at onset, preclinical cognitive and motor functioning, disease progression, duration of illness, behavioural functioning, and availability of effective treatment which could be incorporated into genetic counselling in the future.

12. Prenatal testing

Planning a family has been cited as one of the most important reasons to consider predictive testing. Identified carriers have the option of prenatal testing and – more recently – preimplantation genetic testing, yet the results of several studies have shown a low uptake of prenatal testing and alternative repro-

ductive options [8,19,33,39]. A European collaborative study examined whether the predictive test result had a direct impact on reproductive decision-making [19]. This study found that identified carriers had significantly fewer post-result pregnancies than non-carriers. An Australian study found no differences between carriers and non-carriers [38]. Variation between countries in the uptake of prenatal testing by carriers has also been reported: uptake was lower in the Canadian study by Creighton et al. [8] and in the Dutch study by Maat-Kievit et al. [33] than in the European collaborative study. However, there were also variations within the European study, with more than twice as many prenatal tests performed in the Netherlands than in the other five countries combined. Proposed explanations for this variation have included differences in counselling approaches between countries, greater optimism in some countries about treatment prospects and varying influence of cultural and religious attitudes to pregnancy termination [8,19]. One explanation for the rather low uptake is that couples may feel very reluctant to undergo termination of an affected pregnancy. This reluctance may have increased since the discovery of the HD mutation in 1993, which has obviously provided an outlook for effective future treatments [38]. After in-depth discussion about the couple's intentions regarding pregnancy termination, and the possible consequences of prenatal testing, many couples may decide not to proceed with such testing.

13. Support to carriers

Since the advent of predictive testing the question has been raised as to what we can offer to support carriers of an untreatable disorder and their families? Several authors have contributed – based on their research findings – to the development of a strategy. First, it is important to maximize the feeling of autonomy and connectedness for all involved in the (future) disease process [42]. Second, all efforts should be made to minimize skewdness in relationships, which means that the dynamics of the marital relationship and extended family needs to considered [14]. Specifically, the future change of marital roles, as the disease progresses, needs to be addressed. Richards even suggested the assessment of the marital relationship before disclosure of the test result to explore how the relationship meets the requirements of either test result [40]. Anyhow, open communication between partners and within the family should be encouraged, as there is evidence that open communication is associated with well being [14,52]. Thirdly, awareness of the possible impact on current and future phases of family and individual life cycles needs to be increased to enhance the feeling of control [4,41].

14. Huntington's disease and the life-cycle orientation

HD is a family disorder [4,41]. The initial onset of symptoms is usually between 30 and 50 years, a period when most people are raising a family. People at risk are generally familiar with the disease from early childhood, knowing the symptoms in the affected parent and/or other family members. The presence of HD in a family involves specific stressors, which might influence the relationship between parents and their children for different reasons. First, the affected parent in the onset phase of HD may become preoccupied with the diagnosis, their own future, and the frightening recollections of his/her parent or other relatives going through the HD disease progression. As the disease progresses, the patient is less receptive to the questions of the children and may become depressed or aggressive. These mood and personality changes, together with the choreic movements, may frighten or alienate their offspring. Second, the disease may lead to changes in the family system. The unaffected parent will experience a change in responsibilities and dependency of the spouse in the relationship; the affected spouse insidiously becomes a person who needs care. Some healthy partners may feel unable to take up this task and will leave the household. Changes in the household may lead to neglect of the children. Some children may take up the care of the sick parent. The unaffected parent may seek one of the children as a substitute partner [23]. Third, the fact that the children are at risk for developing HD also puts stress on parent–child bonding. The parents may be concerned about the carrier status of the child and may have feelings of guilt at having passed on the gene. Knowing that their children may get the disease can also create an emotional distance [20]. Some parents also have predictions or even fantasies about their children, thinking that they may or may not develop HD [26]. The healthy parent often has the difficult task of rearing these children and informing them about their risk without the help of the partner. To summarise, a family burdened by a genetic disorder may have to deal with several types of loss: loss of the physical capacity of the affected person, loss of his or her own personality, loss of the old family system, and loss through death. This may be accompanied by shame, secretiveness, and social isolation. Folstein et al. investigated how childhood experiences contribute to a more or less favourable adaptation in later life [21]. They found conduct disorder in adolescents and antisocial personality disorder in adults to be related to experiences of having lived in a disorganised household. Decruyenaere et al. found a low but significant correlation between the participants' age at which the parent showed the first symptoms and psychological functioning before test disclosure [10]; however, psychological adjustment to the test result was not correlated with the age of the participant at onset of HD in the parent. To identify adjustment problems in adult risk carriers, childhood experiences and family dynamics need to be taken into account. Clinicians have shown how the presence of HD in a family can affect the family dynamics [27,29]. In some of the reviewed studies, the influence of HD on family dynamics can be inferred. Post-test studies indicated the difficult and different processes test participants and their partners go through. Marriage and career need to be reconsidered and the necessary social support may no longer be available. Having children is an additional stress factor for both carriers and their partners. People need to learn to live with anticipatory loss and uncertainty. A carrier and his family need to find a balance between open communication and proactive planning with the need to live a normal life, keeping threatened illness in perspective. Finally, tested people might benefit from maintaining up-to-date genetic and medically relevant information.

References

[1] E.W. Almqvist, M. Bloch, R. Brinkman, D. Craufurd, M.R. Hayden, A worldwide assessment of the frequency of suicide, suicide attempts, or psychiatric hospitalization after predictive testing for Huntington disease [see comments], Am. J. Hum. Genet. 64 (1999) 1293–1304.

[2] E.W. Almqvist, R.R. Brinkman, S. Wiggins, M.R. Hayden, Psychological consequences and predictors of adverse events in the first 5 years after predictive testing for Huntington's disease, Clin. Genet. 64 (2003) 300–309.

[3] M. Broadstock, S. Michie, T. Marteau, Psychological consequences of predictive genetic testing: a systematic review, Eur. J. Hum. Genet. 8 (2000) 731–738.

[4] A. Brouwer-Dudok de Wit, A. Savenije, M. Zoeteweij, A. Maat-Kievit, A. Tibben, A hereditary disorder in the family and the family life cycle: Huntington disease as a paradigm, Family Process 41 (2002) 677–692.

[5] A.M. Codori, J. Brandt, Psychological costs and benefits of predictive testing for Huntington's disease, Am. J. Med. Genet. 54 (1994) 174–184.

[6] A.M. Codori, R. Hanson, J. Brandt, Self-selection in predictive testing for Huntington's disease [see comments], Am. J. Med. Genet. 54 (1994) 167–173.

[7] A.M. Codori, P.R. Slavney, C. Young, D.L. Miglioretti, J. Brandt, Predictors of psychological adjustment to genetic testing for Huntington's disease, Health Psychol. 16 (1997) 36–50.

[8] S. Creighton, E.W. Almqvist, D. Macgregor, B. Fernandez, H. Hogg, J. Beis, J.P. Welch, C. Riddell, R. Lokkesmoe, M. Khalifa, J. MacKenzie, A. Sajoo, S. Farrell, F. Robert, A. Shugar, A. Summers, W. Meschino, D. Allingham-Hawkins, T. Chiu, A. Hunter, J. Allanson, H. Hare, J. Schween, L. Collins, S. Sanders, C. Greenberg, S. Cardwell, E. Lemire, P. MacLeod, M.R. Hayden, Predictive, pre-natal and diagnostic genetic testing for Huntington's disease: the experience in Canada from 1987 to 2000, Clin. Genet. 63 (2003) 462–475.

[9] M. Decruyenaere, G. Evers-Kiebooms, A. Boogaerts, J.J. Cassiman, T. Cloostermans, K. Demyttenaere, R. Dom, J.P. Fryns, H. Van den Berghe, Predictive testing for Huntington's disease: risk perception, reasons for testing and psychological profile of test applicants, Genet. Counseling 6 (1995) 1–13.

[10] M. Decruyenaere, G. Evers-Kiebooms, A. Boogaerts, J.J. Cassiman, T. Cloostermans, K. Demyttenaere, R. Dom, J.P. Fryns, Psychological functioning before predictive testing for Huntington's disease: the role of the parental disease, risk perception, and subjective proximity of the disease, J. Med. Genet. 36 (1999) 897–905.

[11] M. Decruyenaere, G. Evers-Kiebooms, A. Boogaerts, T. Cloostermans, J.J. Cassiman, K. Demyttenaere, R. Dom, J.P. Fryns, B.H. Van den, Non-participation in predictive testing for Huntington's disease: individual decision-making, personality and avoidant behaviour in the family, Eur. J. Hum. Genet. 5 (1997) 351–363.

[12] M. Decruyenaere, G. Evers-Kiebooms, A. Boogaerts, K. Demyttenaere, R. Dom, J.P. Fryns, Partners of mutation-carriers for Huntington's disease: forgotten persons? Eur. J. Hum. Genet. 13 (2005) 1077–1085.

[13] M. Decruyenaere, G. Evers-Kiebooms, T. Cloostermans, A. Boogaerts, K. Demyttenaere, R. Dom, J.P. Fryns, Psychological distress in the 5-year period after predictive testing for Huntington's disease, Eur. J. Hum. Genet. 11 (2003) 30–38.

[14] M. Decruyenaere, G. Evers-Kiebooms, T. Cloostermans, A. Boogaerts, K. Demyttenaere, R. Dom, J.P. Fryns, Predictive testing for Huntington's disease: relationship with partners after testing, Clin. Genet. 65 (2004) 24–31.

[15] M. Dozier, S.W. Lee, Discrepancies between self- and other-report of psychiatric symptomatology: effects of dismissing attachment strategies, Dev. Psychopathol. 7 (1995) 217–226.

[16] A.C. DudokdeWit, A. Tibben, H.J. Duivenvoorden, M.F. Niermeijer, J. Passchier, Predicting adaptation to presymptomatic DNA testing for late onset disorders: who will experience distress? Rotterdam Leiden Genetics Workgroup, J. Med. Genet. 35 (1998) 745–754.

[17] A.C. DudokdeWit, A. Tibben, H.J. Duivenvoorden, M.F. Niermeijer, J. Passchier, R.W. Trijsburg, Distress in individuals facing predictive DNA testing for autosomal dominant late-onset disorders: comparing questionnaire results with in-depth interviews. Rotterdam/Leiden Genetics Workgroup, Am. J. Med. Genet. 75 (1998) 62–74.

[18] G.M.D. Duisterhof, R.W. Trijsburg, M.F. Niermeijer, R.A.C. Roos, A. Tibben, Psychological studies on Huntington's disease: making up the balance, J. Med. Genet. 38 (2001) 852–861.

[19] G. Evers-Kiebooms, K. Nys, P. Harper, M. Zoeteweij, A. Durr, G. Jacopini, C. Yapijakis, S. Simpson, Predictive DNA-testing for Huntington's disease and reproductive decision making: a European collaborative study, Eur. J. Hum. Genet. 10 (2002) 167–176.

[20] J.H. Fanos, Developmental tasks of childhood and adolescence: implications for genetic testing, Am. J. Med. Genet. 71 (1997) 22–28.

[21] S.E. Folstein, M.L. Franz, B.A. Jensen, G.A. Chase, M.F. Folstein, Conduct disorder and affective disorder among the offspring of patients with Huntington's disease, Psychol. Med. 13 (1983) 45–52.

[22] C. Goizet, G. Lesca, A. Durr, Presymptomatic testing in Huntington's disease and autosomal dominant cerebellar ataxias, Neurology 59 (2002) 1330–1336.

[23] M.B. Hans, A.H. Koeppen, Huntington's chorea. Its impact on the spouse, J. Nerv. Ment. Dis. 168 (1980) 209–214.

[24] P.S. Harper, C. Lim, D. Craufurd, Ten years of presymptomatic testing for Huntington's disease: the experience of the UK Huntington's Disease Prediction Consortium, J. Med. Genet. 37 (2000) 567–571.

[25] IHA/WFN, International Huntington Association and the World Federation of Neurology Research Group on Huntington's Chorea. Guidelines for the molecular genetics predictive test in Huntington's disease. J. Med. Genet. 31 (1994) 555–559.

[26] S. Kessler, Invited essay on the psychological aspects of genetic counselling. V. Preselection: a family coping strategy in Huntington disease, Am. J. Med. Genet. 31 (1988) 617–621.

[27] S. Kessler, Forgotten person in the Huntington disease family, Am. J. Med. Genet. 48 (1993) 145–150.

[28] S. Kessler, Predictive testing for Huntington disease: a psychologist's view [editorial; comment], Am. J. Med. Genet. 54 (1994) 161–166.

[29] S. Kessler, M. Bloch, Social system responses to Huntington disease, Family Process 28 (1989) 59–68.

[30] F. Laccone, U. Engel, E. Holinski-Feder, M. Weigell-Weber, K. Marczinek, D. Nolte, D.J. Morris-Rosendahl, C. Zuhlke, K. Fuchs, H. Weirich-Schwaiger, G. Schluter, G. von Beust, A.M. Vieira-Saecker, B.H. Weber, O. Riess, DNA analysis of Huntington's disease: 5 years of experience in Germany, Austria, and Switzerland, Neurology 53 (1999) 801–806.

[31] D.R. Langbehn, R.R. Brinkman, D. Falush, J.S. Paulsen, M.R. Hayden, A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length, Clin. Genet. 65 (2004) 267–277.

[32] A. Maat-Kievit, M. Losekoot, K. Zwinderman, M. Vegter-van der Vlis, R. Belfroid, F. Lopez, G.J. van Ommen, M. Breuning, R. Roos, Predictability of age at onset in huntington disease in the Dutch population, Medicine (Baltimore) 81 (2002) 251–259.

[33] A. Maat-Kievit, M. Vegter-van der Vlis, M. Zoeteweij, M. Losekoot, A. van Haeringen, H. Kanhai, R. Roos, Experience in prenatal testing for Huntington's disease in The Netherlands: procedures, results and guidelines (1987–1997), Prenatal Diagnosis 19 (1999) 450–457.

[34] A. Maat-Kievit, M. Vegter-van der Vlis, M. Zoeteweij, M. Losekoot, A. Haeringen van, R.A.C. Roos, Paradox of a better test for Huntington's disease, J. Neurol. Neurosurg. Psychiatry 69 (2000) 579–583.

[35] B. Meiser, S. Dunn, Psychological impact of genetic testing for Huntington's disease: an update of the literature, J. Neurol. Neurosurg. Psychiatry 69 (2000) 574–578.

[36] K.A. Quaid, M.K. Wesson, Exploration of the effects of predictive testing for Huntington disease on intimate relationships, Am. J. Med. Genet. 57 (1995) 46–51.

[37] M.A. Ramos-Arroyo, S. Moreno, A. Valiente, Incidence and mutation rates of Huntington's disease in Spain: experience of 9 years of direct genetic testing, J. Neurol. Neurosurg. Psychiatry 76 (2005) 337–342.

[38] F. Richards, Couples' experiences of predictive testing and living with the risk or reality of Huntington disease: a qualitative study, Am. J. Med. Genet. A 126 (2004) 170–182.

[39] F.H. Richards, G. Rea, Reproductive decision making before and after predictive testing for Huntington's disease: an Australian perspective, Clin. Genet. 67 (2005) 404–411.
[40] F. Richards, K. Williams, Impact on couple relationships of predictive testing for Huntington disease: a longitudinal study, Am. J. Med. Genet. A 126 (2004) 161–169.
[41] J.S. Rolland, J.K. Williams, Toward a biopsychosocial model for 21st-century genetics, Family Process 44 (2005) 3–24.
[42] S.K. Sobel, D.B. Cowan, Impact of genetic testing for Huntington disease on the family system, Am. J. Med. Genet. 90 (2000) 49–59.
[43] S. Sobel, C.B. Cowan, Ambiguous loss and disenfranchised grief: the impact of DNA predictive testing on the family as a system, Family Process 42 (2003) 47–57.
[44] M.P. Solis-Perez, J.A. Burguera, F. Palau, L. Livianos, M. Vila, L. Rojo, Results of a program of presymptomatic diagnosis of Huntington's disease: evaluation of a 6-year period, Neurologia 16 (2001) 348–352.
[45] C.A. Taylor, R.H. Myers, Long-term impact of Huntington disease linkage testing, Am. J. Med. Genet. 70 (1997) 365–370.
[46] S.D. Taylor, Demand for predictive genetic testing for Huntington's disease in Australia, 1987–1993, Med. J. Aust. 161 (1994) 351354–351355.
[47] A. Tibben, H.J. Duivenvoorden, M.F. Niermeijer, M. Vegter-van der Vlis, R.A. Roos, F. Verhage, Psychological effects of presymptomatic DNA testing for Huntington's disease in the Dutch program, Psychosom. Med. 56 (1994) 526–532.
[48] A. Tibben, R. Timman, E.C. Bannink, H.J. Duivenvoorden, Three-year follow-up after presymptomatic testing for Huntington's disease in tested individuals and partners, Health Psychol. 16 (1997) 20–35.
[49] A. Tibben, M. Vegter-van der Vlis, M.I. Skraastad, P.G. Frets, J.J. van der Kamp, M.F. Niermeijer, G.J. van Ommen, R.A. Roos, H.G. Rooijmans, D. Stronks, et al., DNA-testing for Huntington's disease in The Netherlands: a retrospective study on psychosocial effects, Am. J. Med. Genet. 44 (1992) 94–99.
[50] R. Timman, R. Roos, A. Maat-Kievit, A. Tibben, Adverse effects of predictive testing for Huntington disease underestimated: long-term effects 7–10 years after the test, Health Psychol. 23 (2004) 189–197.
[51] I.M. van der Steenstraten, A. Tibben, R.A. Roos, J.J. van de Kamp, M.F. Niermeijer, Predictive testing for Huntington disease: nonparticipants compared with participants in the Dutch program, Am. J. Hum. Genet. 55 (1994) 618–625.
[52] I. van Oostrom, H. Meijers-Heijboer, L.N. Lodder, H.J. Duivenvoorden, A.R. van Gool, C. Seynaeve, C.A. van der Meer, J.G. Klijn, B.N. van Geel, C.W. Burger, J.W. Wladimiroff, A. Tibben, Long-term psychological impact of carrying a BRCA1/2 mutation and prophylactic surgery: a 5-year follow-up study, J. Clin. Oncol. 21 (2003) 3867–3874.
[53] World Federation of Neurology: Research Committee. Research Group on Huntington's chorea. Ethical issues policy statement on Huntington's disease molecular genetics predictive test. J. Neurol. Sci. 94 (1989) 327–332.